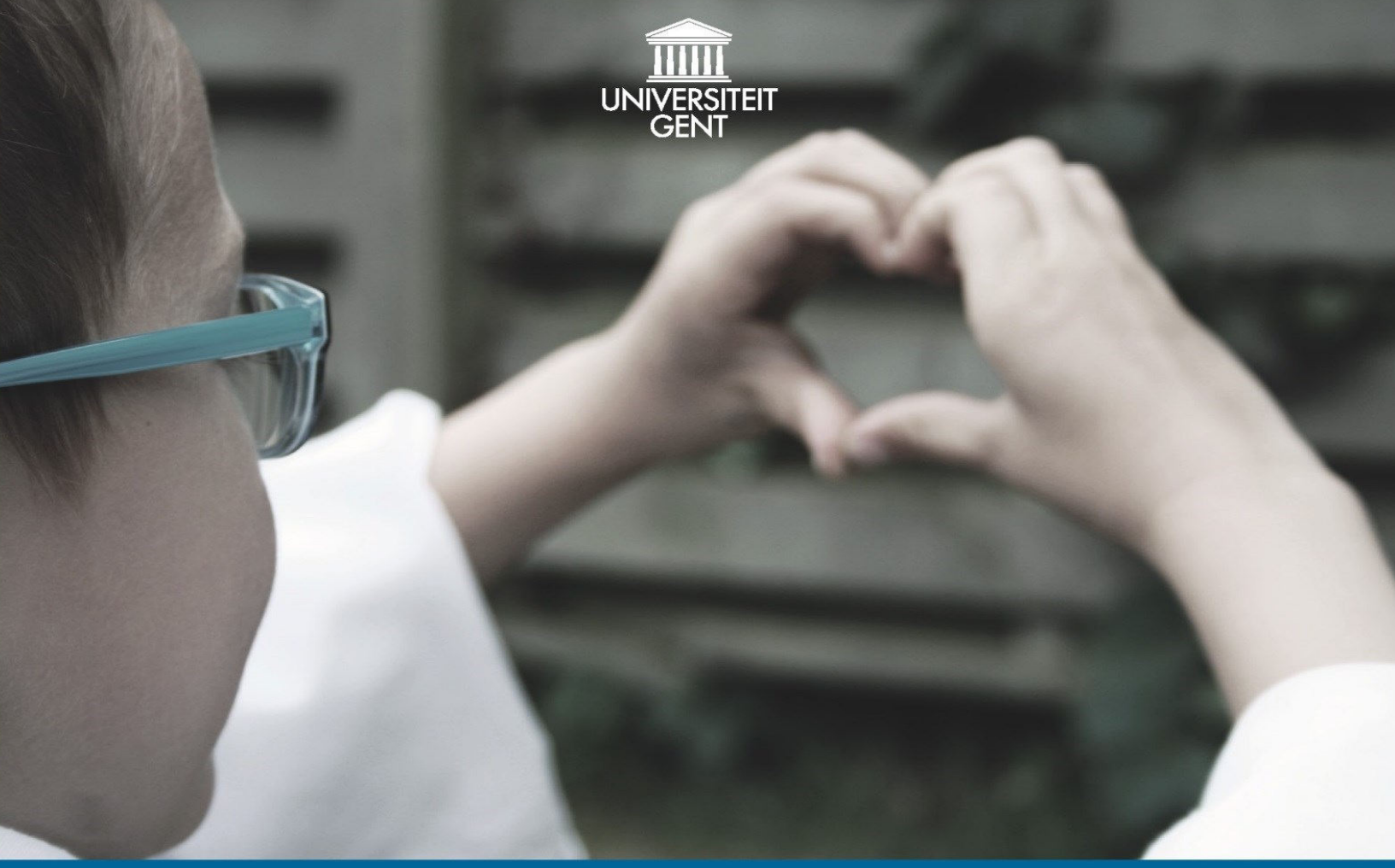

UNIVERSITEIT GENT

2015 | Faculty of Medicine and Health Sciences

NEURODEVELOPMENTAL OUTCOME AND BEHAVIOR IN CHILDREN TREATED FOR CONGENITAL HEART DISEASE

Doctoral dissertation submitted in fulfillment of the requirements for the degree of
Doctor in Medical Sciences

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FACULTY OF **MEDICINE AND HEALTH SCIENCES**

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2015

UNIVERSITEIT GENT

LABORATORY FOR NEUROPSYCHOLOGY

UZ Universitair Ziekenhuis Gent

UZ LEUVEN

Universiteit Gent, Belgium
ISBN 978-94-6197-334-4

This project was funded by the Fund for Scientific Research, Flanders [G.0095.09N] and sponsored by Mardi Consult BVBA.

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Voor mijn ouders
&
Oma

The mind determines what's possible.
The heart surpasses it.

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THESIS AT A GLANCE

THESIS at a glance				
	Aim/ objective	**Material/ methods**	**Results**	**Conclusions**
Study I. ***Neurobehavioral functioning in school-aged children with a corrected septal heart defect*** **Published –** **Acta Cardiologica 2013; 68 (1): 23-30**	To explore neurobehavioral consequences after surgical treatment for acyanotic congenital heart defect at the age of 5 to 12 years.	N = 15 WISC-III-NL NePsy CBCL Self-perception questionnaire ASD-II or VSD were screened. Patients were compared with matched healthy controls.	Estimated intelligence scores were in the average range. Domains of attention and fine motor skills, and the subtest level of language abilities, elicited significant group differences, with less favourable outcomes for the patient group. Parents of patients reported more withdrawn behavior, social difficulties, thought problems, attentional shortcomings and lower competence for activities. These parents also indicated poor problem solving skills in everyday activities.	Surgical patients displayed subtle neuropsychological difficulties concerning language and fine motor skills. Behavioral difficulties were common
Study II. ***Neurodevelopmental outcome after surgery for acyanotic congenital heart disease*** **In Press –** **Research in Developmental Disabilities 2015; 45: 58-68**	To describe the neuropsychological profile of children with acyanotic CHD and explore medical correlates	N=46 WISC-III NePsy-II-NL CBCL Medical charts Acyanotic CHD patients were divided following diagnosis (ASD-II or VSD) Outcomes were compared between patient groups and with healthy matched controls. Hospitalization variables were retrieved to explore associations with cognitive outcome.	ASD-II patients had lower scores in domains of visuospatial processing, language, attention, and social perception. VSD patients displayed subtle problems in attention and visuospatial information processing. Only few perioperative medical factors, but also socioeconomic variables were linked to cognitive outcomes. Parents of ASD-II patients reported more school problems compared to controls.	Subtle cognitive difficulties can emerge in domains of visuospatial information processing, language, attention, and social perception. These shortcomings might hamper school performances, suggested by lower school competence ratings as indicated by parents. Ongoing follow-up and cognitive screening is warranted to promote developmental progress, in which both parents and clinicians share responsibility.

THESIS at a glance				
	Aim/ objective	**Material/ methods**	**Results**	**Conclusions**
Study III. ***Neurodevelopment and Behavior after Transcatheter versus Surgical Closure of Secundum Type Atrial Septal Defect*** **Published –** **The Journal of Pediatrics 2015; 166(1):31-38**	To assess the neuropsychological and behavioral profiles of school-aged children treated for atrial septal defect, secundum type (ASD-II) with open-heart surgery or catheterization.	N= 48 WISC-III NePsy-II-NL CBCL Medical charts Patients and a matched healthy group were evaluated. Hospitalization variables were retrieved from medical files for studying associations with long-term neurodevelopment.	Compared with the healthy matched controls, patients treated for ASD-II had significantly lower scores on subtasks of attention and executive Functioning, language, working memory, sensorimotor functioning, social cognition, and visuospatial information processing. Only subtle differences, mainly in visuospatial Information processing were found between the surgical repair and transcatheter repair groups. SES, longer hospital stay, and larger defect size were associated with neurocognitive outcome measures. Parents of patients reported more thought problems, posttraumatic stress problems, and lower school performance compared with parents of healthy peers.	After treatment for ASD-II, children display a range of neuropsychological difficulties that may increase the risk for learning problems and academic underachievement. Differences related to treatment were not found. Our results suggest that neurodevelopmental and behavioral follow-up at school-age is warranted in this group.

THESIS at a glance				
	Aim/objective	**Material/ methods**	**Results**	**Conclusions**
Study IV. ***Neurocognitive development and behavior in school-aged children after surgery for univentricular or biventricular congenital heart disease*** **Published-** **The European Journal of Cardio-Thoracic Surgery; doi:10.1093/ejcts/ezv029**	To assess the long-term neuropsychological and behavioral profile of school-aged children who were treated for univentricular heart conditions (UVH) or biventricular congenital heart defects (BiVH) in infancy in a cross-sectional study design.	N=63 WISC-III NePsy-II-NL CBCL Medical charts Outcomes of UVH, BiVH patients, and UVH-Controls Associations between cognitive outcome, medical and SES were explored.	Mean intelligence and neuropsychological scores were found within normal ranges for all diagnostic groups. Significant differences between UVH patients and controls emerged on auditory sustained and alternating attention, fine motor skills, visuospatial information processing, and to a lesser extent, memory performance. Parents of UVH patients reported more externalizing problems and school problems. Patient groups did not differ on neuropsychological outcome measures, nor on behavioral problems as rated by parents.	After Fontan completion, patients at school-age display intelligence scores within normal population-based ranges. However, they were found at risk for subtle shortcomings in attention, fine motor skills, visuospatial information processing, and externalizing behavior problems.
Study V. ***Long-term behavioral and emotional outcomes in school-aged children following invasive treatment for congenital heart disease a multicenter experience*** **[Submitted Manuscript]**	To assess the occurrence of behavioral and emotional problems at school-age using parental reports after surgical or catheter-based treatment for various forms of congenital heart disease (CHD) in infancy.	N=94 CBCL Questionnaire on cognition, motor and emotional functioning	Parents of CHD patients reported significantly more problems in all domains addressed in the cognitive and emotional questionnaire. Parents of patients reported significantly higher scores for various problem scales, mostly in the internalizing problem behavior spectrum, compared to the reference group. CHD parents also indicated reduced school performance, more special education, repeated a school year more often, and experienced school problems.	Overall, although modern medical management of CHD has excellent functional results, parents of CHD children reported persisting higher levels of behavioral and emotional problems compared to parents of a matched control group. Assessing psychosocial adjustment in children treated for CHD can be helpful to detect children at higher risk for academic underachievement and possible psychopathology.

CHAPTER 1
GENERAL INTRODUCTION

GENERAL INTRODUCTION

The birth prevalence of children born with a congenital heart disease (CHD) is 8.3 per 1000 births, of which one-third will require medical intervention[1]. Despite invasive treatment, mortality in this group remains substantial. Eurocat recorded overall perinatal mortality (mainly first week mortality) associated with CHD to be as high as 22.6% in Europe between 2008-2012[2]. As a result of medical, surgical, technical advances and improved monitoring in the pediatric intensive care unit, survival rates for this condition are improving. With this growing number of survivors, subsequent neurodevelopmental impairments are increasingly recognized as significant components of late morbidity.

The etiology of these neurocognitive sequelae is assumed to be multifactorial, with preoperative, perioperative and postoperative factors contributing to long-term outcome. Even if intraoperative techniques in neonates and infants are state-of-the-art and lifesaving, these procedures may carry intrinsic risk factors for neurologic injury of the immature brain. Previous research primarily focused on perioperative support procedures such as cardiopulmonary bypass (CPB), deep hypothermic circulatory arrest (DHCA), acid base management, and hemodilution during CPB as causal factors for adverse neuropsychological functioning.

In this first chapter, early and contemporary literature concerning late neurodevelopmental outcome in children treated for CHD is reviewed. Further on, medical parameters and other possible predictors are discussed in relation to neurocognitive development. Study aims and the rationale are set out in chapter 2. Five manuscripts, the core of this thesis, are next, and a final summary of the main findings, limitations and directions for future research will be presented.

INTRODUCTION

1. Congenital heart disease

Congenital heart disease is a structural anomaly of the heart or the great vessels that may have disruptive effects on the circulatory system and may require surgical or catheter-based treatment. A population-based study conducted in Belgium demonstrated a birth prevalence of CHD of 8.3 per 1,000 births[1], closely adhering to the worldwide stable estimate of 9 per 1,000 live births in the last 15 years[3]. Up to one-third (39%) of these diagnosed children require interventional repair early in life[1]. Advances in diagnostic and cardio-surgical techniques, medical treatment and nursing care have resulted in a notable decline in mortality rates[4]. Concurring genetic, syndromic or other non-cardiac conditions are common and may complicate care and alter treatment[5].

Parallel with this improved prognosis and treatment, it became clear that surviving children treated for CHD often display a distinctive pattern of adverse neurodevelopment, and reveal behavioral and emotional problems that are considered significant components of late morbidity[6]. The integrity of the CHD patients' nervous system is questioned since susceptibility of brain injury, adverse effects of perioperative events, and neurodevelopmental sequelae are increasingly recognized in children treated for CHD in the newborn period or infancy.

1.1. Classification of CHD

Over the years, a number of classifications for CHD have been described[7-9]. We will address the three most relevant within the framework of this doctoral dissertation.

Dysfunctional heart development, resulting in CHD, can occur at different levels of the circulatory circuit and present itself isolated or in various combinations. This is used in the sequential analysis; the main classification used by congenital cardiologists and cardiac surgeons. In summary, the sequential analysis offers the sum of all the different anomalies at every separate level of the cardiac circulation. It allows cardiologists and cardiac surgeons to describe and plan the surgical procedure according to the topological and architectural structures of each individual heart. At first, the atrial situs and venous drainage is determined (situs solitus / situs inversus), followed by the position of the

ventricles and their atrioventricular connections (AV). These AV's can be biventricular, when each atrium is connected to a ventricle, or it can be univentricular when the connection (right or left) is absent (tricuspid valve atresia and mitral valve atresia, respectively), or there is a double inlet from both atria draining into one single ventricle through two AV valves. The sequence of this approach is completed with defining ventriculoarterial connections (VA). A concordant VA connection is established when the pulmonary artery originates in the right ventricle and the aorta in the left ventricle, while a discordant VA connection reverses these connections. Double outlet or single outlet VA connections are defined by both great arteries arising from only one ventricular cavity, or when only a patent great artery arises from the heart respectively. Although this way of classification is widely used by cardiac specialists, this method is too detailed to classify the congenital heart defects considered in this doctoral dissertation.

Another way to sort various forms of CHD is the patho-physiological classification, allowing health care providers to establish an initial treatment procedure to stabilize the condition.

The first class in this approach encompasses CHD's with predominant left-to-right shunts ensuing ventricular volume and/or pressure overload. In a ventricular septal defect (VSD), oxygenated blood shunts from left to right causing a progressive dilatation of the left ventricle caused by volume overload and eventually pulmonary hypertension (pressure overload). Depending of the size of the defect, this results in symptoms such as progressive exercise intolerance, dyspnea, and severe heart failure. Septal defects such as atrial or ventricular septal defects (ASD or VSD), patent ductus arteriosus (PDA), and atrioventricular septal defects (AVSD), and complete common atrioventricular canal defect (CAVC) are part of this classification, as is the univentricular heart with unprotected pulmonary circulation.

The next class consists of septal defects combined with a significant obstruction to pulmonary flow. This right-to-left shunting causes cyanosis, a bluish discoloration of the skin due to deoxygenated blood entering the systemic circulation. Defects such as pulmonary valve stenosis with ASD, pulmonary valve stenosis with VSD (Tetralogy of Fallot - TOF), tricuspid atresia (TA), Ebstein anomaly of the tricuspid valve, and single ventricle with pulmonary stenosis qualify for this class. A second category in this class encompasses CHD's with

parallel systemic and pulmonary circulations. Complete transposition of the great arteries (TGA), in which the aorta originates from the right ventricle causing deoxygenated blood flow through the aorta and the pulmonary artery originates from the left ventricle directing oxygenated blood again to the lungs. (Isolated) cyanosis is the main clinical feature of both types of right-left-shunt.

The third category consists of CHD's with left sided obstruction and is further characterized by ventricular pressure overload with concentric myocardial hypertrophy of the left ventricle. Secondary pulmonary hypertension can complicate the clinical picture. Defects that belong in this category are aortic stenosis, pulmonary stenosis, and aortic coarctation. Univentricular hearts with systemic obstruction also belong to this class. The most common is the hypoplastic left heart syndrome (HLHS) consisting of hypoplasia of the left heart, mitral stenosis or atresia, aortic stenosis or atresia, hypoplasia of the ascending aorta and coarctation. Patients with moderate left sided obstruction are often asymptomatic, but patients with severe left sided obstruction present with signs of severe heart failure and are at risk for sudden death.

The last category is miscellaneous and consists of arrhythmias, cardiomyopathies and coronary anomalies.

A last classification that is probably the most relevant for this doctoral dissertation is the one established by Task Force 1 of the 32nd Bethesda Conference of the American College of Cardiology[9] (Table 1). A division in terms of complexity was established. With increasing complexity, these patients are considered to be more vulnerable to additional acquired comorbidities, affecting cardiac and medical care (hypertension, pulmonary, renal, and myocardial disease, coronary artery disease).

Table 1. *Classification of CHD following Task Force 1 of the 32nd Bethesda Conference of the American College of Cardiology*[9].

CHD complexity		
Mild	**Moderate**	**Severe**
Native conditions ○ Isolated congenital aortic valve disease ○ Isolated congenital mitral valve disease (except parachute valve, cleft leaflet) ○ Isolated patent foramen ovale or small atrial septal defect ○ Isolated small ventricular septal defect (no associated lesions) ○ Mild pulmonic stenosis **Repaired conditions** ○ Previously ligated or occluded ductus arteriosus ○ Repaired secundum or sinus venosus atrial septal defect without residua ○ Repaired ventricular septal defect without residua	○ Aorto-left ventricular fistulae ○ Anomalous pulmonary venous drainage (partial or total) ○ Atrioventricular canal defects (partial or complete) ○ Coarctation of the aorta ○ Ebstein's Anomaly ○ Infundibular right ventricular outflow obstruction of significance ○ Ostium primum atrial septal defect ○ Patent ductus arteriosus (not closed) ○ Pulmonary valve regurgitation (moderate to severe) ○ Pulmonic valve stenosis (moderate to severe) ○ Sinus of Valsalva fistula/aneurysm ○ Sinus venosus atrial septal defect ○ Subvalvar or supravalvar aortic stenosis (except HOCM = hypertrophic obstructive cardiomyopathyTetralogy of Fallot ○ Ventricular septal defect with -Absent valve or valves -Aortic regurgitation -Coarctation of the aorta -Mitral Disease -Right ventricular outflow tract obstruction -Straddling tricuspid/mitral valve -Subaortic stenosis	○ Conduits, valved or nonvalved ○ Cyanotic congenital heart disease (all forms) ○ Double-outlet ventricle ○ Eisenmenger syndrome ○ Fontan procedure ○ Mitral Atresia ○ Single Ventricle (also called double inlet or outlet, common or primitive) ○ Pulmonary Atresia (all forms) ○ Pulmonary vascular obstructive diseases ○ Transposition of the Great Arteries - D Type ○ Transposition of the Great Arteries -L Type (Congenitally Corrected TGA) ○ Tricuspid Atresia Truncus arteriosus/hemitruncus ○ Other abnormalities of atrioventricular or ventriculoarterial connection not included above (i.e. criss-cross heart, isomerism, heterotaxy syndromes)

1.2. Treatment

More than 1 in three children diagnosed with CHD needs catheterization or a cardio surgical intervention following the nature of the condition, while others are asymptomatic with spontaneous resolution of the lesion and medical intervention is not required[1].

Symptomatic mild defects such as isolated septal defects can be corrected by biventricular repair techniques. Depending on size and location, these defects are corrected by transcatheter guided closure with a device (mostly small defects) or through a single open heart surgery with midline sternotomy and direct suture or patch closure of the defect under general anesthesia and cardiopulmonary bypass. Even anomalies classified as moderate or severe can be treated with surgical biventricular techniques, but often need the insertion of conduits, valve conduits or prosthetic valves. Expert cardiologic care for those afflicted with more complex univentricular hearts, such as hypoplastic left heart or tricuspid atresia, necessitate a series of 'palliative' surgical procedures[10]. In these conditions, one ventricle has to sustain both systemic and pulmonary circulation, leading to ventricular pressure and volume overload and inadequate organ perfusion (Fig 1). Instead of a straightforward corrective biventricular procedure, univentricular palliation involves a step-wise surgical approach aimed at relieving the symptoms, improving the abnormal heart function, and preparing the circulatory system for the ultimate Fontan-type repair when the child reaches an age and body weight suitable for these more advanced surgical techniques. In the case of a hypoplastic left heart, surgical palliation is initialized with the Norwood procedure, subsequently followed by the bi-directional Glenn procedure and completed with the Fontan circulation(Fig 2)[10]. Tricuspid atresia is mostly palliated through a Blalock-Taussig shunt or pulmonary artery banding, followed by a hemi-Fontan and completion of the Fontan circulation. The Fontan circulation consists of a direct connection of the systemic veins to the pulmonary arteries, creating a pulmonary circulation without a pump (right ventricle). The pulmonary venous blood enters the ventricle which is only connected to the aorta and supports the systemic circulation.

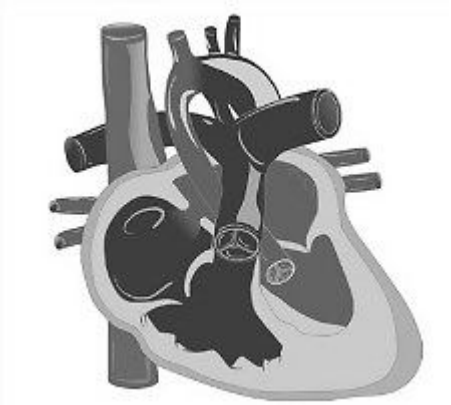

Fig 1. *Anatomy of the hypoplastic left heart. In view of mitral atresia, the blood in the left atrium shunts across atrial septal defect to the right atrium. Blood flow to the aorta is supplied through the ductus arteriosus.*

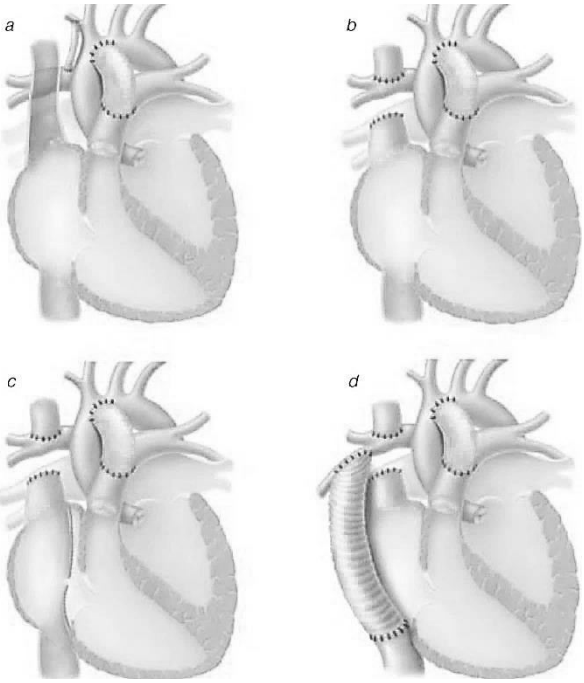

Fig 2. a. *The Norwood operation establishes a neo-aorta, connecting the distal pulmonary artery to a systemic shunt, usually a modified Blalock-Taussig shunt.* **b.** *The Bidirectional Glenn-procedure involves disconnecting the previously placed shunt to the pulmonary arteries and anastomosis of the superior vena cava to the pulmonary artery.* **c.** *The completion of the circuit is the Fontan operation in which the inferior vena cava is connected to the pulmonary artery through the right atrium or* **d.** *via extra-cardiac conduit connecting the inferior vena cava to the pulmonary artery directly*

Obviously this description of available procedures for the surgical management of CHD is not complete, we refer the interested reader to more comprehensive descriptions of pediatric cardiac and surgical care[11].

2. Neurodevelopmental sequelae after treatment for CHD

2.1. Neuropsychological functioning

There are six key domains of neurocognitive functions, with their own subdomains (Table 2). These domains are also defined by the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5)[12], and can help establish the aetiology and severity of possible neurocognitive disorders. Subtests of neuropsychological test batteries are theoretically derived from such domains to assess neurocognitive capacities related to disorders that are typically diagnosed in childhood, which are required for academic success[13].

Table 2. *Neurocognitive domains*

Neurocognitive domain	Subdomains	Assessment
Complex attention	*Sustained attention, divided attention, selective attention, processing speed*	*Maintenance of attention over time; maintenance of attention despite competing stimuli; attending to two tasks within the same time period respectively*
Executive function	*Planning, decision making, working memory, responding to feedback/error correction, overriding habits/inhibition, mental flexibility*	*Interpret a sequential picture or object arrangement; performance of tasks that assess process of deciding in the face of competing alternatives; ability to hold and manipulate information for a brief period; ability to shift between two concepts, tasks, or response rules*
Language	*Expressive language and receptive language*	*Identification of objects or pictures; word fluency; grammar and syntax; Comprehension and performance after verbal instructions*
Learning and memory	*Immediate memory, recent memory, very-long-term memory [semantic; autobiographical], implicit learning*	*Ability to repeat a list of words or digits; process of encoding new information, recognizing and recalling of this information*
Social cognition	*Recognition of emotions, theory of mind-insight*	*Identification of positive or negative affect in images of faces; Ability to consider another person's mental state (thoughts, desires, intentions)*
Perceptual-motor	*Visual perception, visuo-constructional abilities, perceptual-motor, praxis, and gnosis*	*hand-eye coordination; integrating perception and movement; imitate gestures; Perceptual integrity of awareness and recognition, such as recognition of faces and colors*

Intermediate and long-term outcomes from various cohorts of patients with CHD have been explored and described in detail. Early reports on neurodevelopmental sequelae mainly focused on clinical populations that had specific delineated diagnoses to allow for a proper evaluation of the effect of the congenital cardiac anomaly (and its treatment characteristics); d-TGA, TOF, and HLH[14-17].

At **preschool-age**, basic cognitive and psychomotor functions are reliably assessed by the Bayley Scales of Infant Development (BSID)[18]**.** This screening tool was developed to evaluate the developmental stage of infants and toddlers (1-42 months), and is widely used in the assessment of children treated for CHD. This assessment tool yields a separate mental and psychomotor developmental index (MDI and PDI), with standardized scores with a mean of 100 and an SD of 15. From the age of 3-4, more cognitive functions can be assessed by intelligence scales (Wechsler Scales) and broad neuropsychological test batteries.

Assessing development at a young age in CHD populations has provided an alarming amount of data that patients diagnosed with CHD perform poorly on early evaluations of mental and motor functioning.

Children treated for CHD have been shown to suffer *motor* impairments consistently over and persisting in time.

Between April 1988 and February 1992, 171 patients were enrolled in a prospective randomized single center trial in Boston to evaluate the temporal neurodevelopmental effects of treatment strategies in patients diagnosed with and treated for d-TGA[19]. Screening at 1 year using the BSID showed a mean MDI of 105.1 (SD 15) and a mean PDI of 95.1 (SD 15.5). Twenty percent of the patients scored less than or equal to 80 for psychomotor functioning. When comparing intraoperative organ support strategies (circulatory arrest or low flow CPB), those assigned to circulatory arrest strategy, had a higher prevalence of lower scores. Follow-up at 4 years showed a developmental profile of basically the continuation of the formerly identified motor deficits together with speech abnormalities and low-to-average intelligence scores[16]**.**

Fuller et al. found a heterogeneous group of patients that underwent CHD-surgery in the neonate or infant period at age 1 to be at risk for neurodevelopmental dysfunction with lower MDI and marked impaired PDI scores compared to normal means[20]. Non-syndromic patients with single ventricle diagnoses, have a

particular risk for obtaining lower PDI scores than controls or patients treated for biventricular CHD[21].

In conclusion, at preschool-age, MDI or mental scores are usually found within one standard deviation from the general population-based mean, reflecting low-to-average scores, while the frequently reported lower PDI scores (1 or 2 SD lower than the reference mean), clearly indicate significant impairments in this domain. Motor abnormalities appear to precede surgical procedures, indicating that intrauterine disturbances affect early outcomes[22]**.** Hypotonia, hypertonia, jitteriness, and motor asymmetries, have been documented in cyanotic and acyanotic CHD cohorts prior to surgery, and neuromotor abnormalities were reported with additional cranial nerve findings (facial palsy, esotropia), choreoathetosis, and seizures after surgery[22].

When reaching **school-age**, cognitive abilities in terms of *intellectual functioning,* and cognition for academic achievement mature.
A few decades ago, IQ-scores were used as sole benchmarks for general mental functioning in cohorts of CHD patients. The earliest reports of mental development in CHD patients documented significantly lower intellience scores than the general population or peers[23, 24]. Over the years, and with medical progress, IQ scores were found to approach population-based norms, although consistently in low-to-average ranges[25-27]**.** Patients with complex CHD are found to be at higher risk for obtaining lower scores in such mental assessments[28, 29], although data are conflicting[17]. Whether or not including certain types of diagnoses, such as HLH, seems to explain these conflicting results.

From a neuropsychological point of view, studies have shown that this clinical cohort manifests mild cognitive impairments in several neuropsychological domains at school-age. Problems in domains of *attention and executive functioning* are well documented.
In the Boston cohort, patients treated for d-TGA assigned to treatment in which low flow CPB was the main support strategy, showed more impulsive task behavior at a mean age of 8 years[25]. Similarly, when assessing alerting, orienting, and executive control using the Attention Network Test, TOF patients at age 5 to 11 years post-surgery obtained significantly lower scores for the executive control

system component (conflict monitoring) when compared to acyanotic CHD and healthy controls. Although not fully reaching statistical significance, VSD patients tended to have a reduced conflict performance when compared with the control group[30]. Miatton et al. also recorded a higher frequency of impulsive test behavior among school-aged children (6-12 years) with cyanotic or acyanotic CHD during the execution of neuropsychological tasks[31]. In patients with a single ventricle, measures of attention, including auditory, visual, and inhibitory processes showed lower scores than the population in up to ~57% of HLH patients, and ~53% in patients with other functional single ventricle lesions. The authors suggested that symptoms underlying attention deficit hyperactivity disorder are particularly prevalent among children with complex CHD[32]. Visconti et al. concluded that surgery for ASD resulted in favourable outcomes on a continuous performance test of attention, while patients treated via catheter-based intervention demonstrated an impulsive task strategy and lower general attentiveness[33].

The Boston series showed that patients treated for d-TGA with cardiac arrest performed worse on measures of *language*, specifically phonologic awareness and verbal fluency[25]. Hövels-Gürich assessed TOF and VSD patients with various language and speech batteries and described a mild degree of oral apraxia (expressive language skills) in 29%, together with a lower prevalence of deficient receptive language functions (6%)[34]. Miatton similarly described expressive and receptive language deficiencies in TOF and acyanotic patients; with lower phonological awareness among the patients, deemed important for reading and spelling skills[15]. In contrast with these findings, Majnemer et al.[35] found receptive language skills to be similar to peers in a heterogeneous group of CHD patients.

Evaluating *memory* in CHD populations, deficiencies have been less pronounced in CHD populations than other neuropsychological domains. Bellinger et al. assessed the Wide range Assessment of Memory and Learning during the d-TGA cohort follow-up at 8 years. Although their memory scores were within normal limits, they performed significantly lower than the expected population means, with the weakest performance on the Design Memory subtest[25]. Miatton et al. reported lower scores for remembering names and a narrative in a TOF cohort, presumably due to dysnomic problems and inefficient retrieval of symbol-

word associations, related to poor language skills[15]. Likewise, Brosig and colleagues[36] assessed the Narrative Memory subtest from the NEPSY and the Recall of Objects subtest from the Differential Ability Scales (DAS) to evaluate memory and learning skills in HLH patients. The latter subtask, measuring visual memory, elicited a significant difference when compared to standardized means. These findings suggest a deficient visual representation of stimuli during memory encoding and retrieval, rather than a verbal basis for information storage in memory processes.

It has been postulated that complex *visuospatial information processing* tasks pose a specific challenge for children with CHD. The experts at Boston Children's Hospital evaluated performances of visual-spatial information processing using tasks for motor control, visual-perceptual abilities, and metacognitive skills in relation to performance on the Rey-Osterrieth Complex Figure (ROCF)[37]. The copy trial was scored for aspects of organization, style, accuracy and error. Fifty-two percent of the d-TGA cohort scored at basal organizational level one, roughly double of the percentage seen in the standard population (22%), and was found related to poor mathematical skills[37]. In the general follow-up study, these Boston patients treated with intraoperative circulatory arrest were less skilled in visual-motor tracking skills at eight years[25] and scored poorer on tasks of visual-spatial information processing at adolescent age[38]. Likewise, other studies showed poor visual-spatial / visual-motor integration when treated for CHD[15, 39], especially in patients with single ventricle circulation[40].

Temporal trends throughout the vast majority of literature in this field on long-term neurodevelopmental follow up of children with CHD have identified persisting and recurring *motor* difficulties and is considered a robust component of late morbidity.
The children enrolled in the Boston trials and treated for d-TGA with circulatory arrest performed significantly poorer on tasks of fine and gross motor skills, had more oromotor and facial movement difficulties, and were less skilled in visual-motor tracking at age 8[25]. Majnemer reported that hallmark features of neurodevelopmental outcomes in a heterogeneous cohort of CHD patients at school-age were defined as fine and gross motor delays, and poor behavioral state

(irritable, lethargic)[35]. A follow-up study of developmental status and exercise capacity at a mean age of ~7 years conducted in Germany, found that in 40 patients operated for TOF and VSD, gross motor dysfunctions were evident in up to 50% and related to preoperative hypoxemia[14]. Another retrospective cohort study identified poorly developed gross and fine motor skills in children with TOF[15]. Children undergoing surgery for complex cardio-pathologies culminating in the Fontan operation, such as single ventricle circulations, have been found to be at a particular risk for poor neuromotor outcomes; adverse fine motor skills such as fingertip tapping and imitating hand positions have been reported[36], next to lower scores for manual dexterity and balance[29] compared to performance of peers.

2.2. Academic functioning

A substantial portion of children treated for CHD have been found to require special services (extra tutoring, speech or physical therapy, occupational support) during their educational curriculum. The Boston trials demonstrated that after cardiac surgery for d-TGA, up to 34% of the total patient cohort required remedial services including speech, occupational, and physical therapy, but also evaluation by a psychiatrist by the age of 8 years. Sixty-five percent of the same cohort in adolescence (mean age ~16 years) had received academic or behavioral services[38]. The Canadian series reported that more than 20% of the children who underwent cardiac surgery in the newborn or infancy period received concurrent educational support or rehabilitation services at school-age[35]. These results suggest that, with the growing number of survivors of complex CHD, persistent school related problems at young age might hamper educational attainment, career options and give rise to poor socio-demographic outcome[41].

2.3. Behavior and socialization

Concerns have arisen regarding the psychosocial and behavioral outcome of CHD children. Internalizing (anxious, depressive, and overcontrolled behavior) and externalizing (aggressive, hyperactive, noncompliant, and undercontrolled behavior) problems as measured by parental or teacher reports have high prevalence in this patient cohort[15, 27]. Experts postulate that poor skills in social cognition[38] and functional limitations in socialization[27] in young children with CHD

are common. Neurodevelopmental and behavioral problems may restrict these children in interpersonal events participation and develop proper socialization skills or autonomy. These findings might implicate a particular proneness for future psychopathology[42]. It remains unclear to what extent these reported problems persist at school-age in an era with modern interventional techniques and improved perioperative care.

This outlined course of broad neurodevelopmental difficulties may eventually affect educational attainment with difficulties in attention and executive functioning, reading and phonemic awareness, mathematics, fine motor skills such as handwriting, and gross motor problems, important for engaging in peer sports. Psychosocial maladjustment may be associated with greater difficulties such as socialization, communicating and self-regulatory behavior. It is thus essential that children at risk for such delays are identified early in childhood so tailored support for these patients and their family can be provided to promote developmental progress. It is important to keep in mind that conflicting data in this field of expertise originate from aspects of different surgical era's, thus excluding the effects of evolving subsequent changes in intraoperative management strategies and perioperative care. Furthermore, the retrospective or prospective character together with the nature of studies (observational or clinical trials) should be accounted for. Lastly, neurodevelopmental testing at young age (before age 6) has only limited predictive value for future academic skills when academic demands tap into higher cognitive functions that were already suboptimal during preschool-age. Since the vast majority of literature focused on developmental outcomes of those with complex cardio-pathologies, the question remains whether patients with mild CHD have the same developmental signature.

3. Etiology and risk stratification

Through significant research efforts, we are starting to understand the complex and multifactorial etiology of these late neurocognitive sequelae. Two main overarching domains seem to interact with each other, resulting in adverse outcomes; biogenetic and environmental influences. The former includes underlying developmental syndromes, genetics, the nature of the heart defect, and the medical/surgical procedures. The latter comprises the situation and environment in which these children grow up; socio-economic status, parenting

style and the social context. These domains are not mutually exclusive as an important interplay exists in which environment can influence biogenetic factors and serve as a protective factor at home, school or work.

3.1. Patient specific and preoperative factors

3.1.1. CHD complexity

It is generally accepted that the risk of developmental delay increases with CHD severity (Figure 1). Children with mild, mostly acyanotic CHD, have a somewhat lower incidence of suboptimal outcome, but findings are contrasting[33, 43]. Moderate, acyanotic or cyanotic CHD are linked to more mild-to-moderate neurocognitive impairments.

Those patients afflicted with complex forms of CHD such as hypoplastic left heart or other univentricular lesions that require complex (staged) surgical interventions are found to perform the poorest on cognitive measures. Their physiology, hemodynamic compromise and the complexity of the surgical treatment are assumed to account for this high risk for developmental delays.

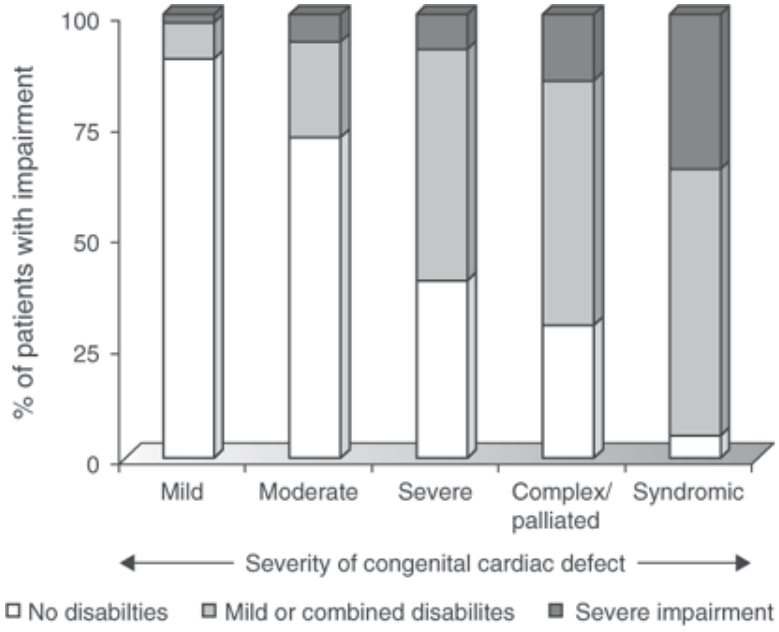

Fig. 3. Schematic representation of developmental abnormalities in children with CHD. *Adapted from Wernovsky[44] with permission of the publisher. Copyright © 2006, Cambridge University Press.*

3.1.2. Birth characteristics

Younger gestational age has been identified as a significant predictor for adverse neurodevelopmental outcomes in CHD populations[45, 46]. At birth and later on, the head circumference of these children is often found smaller than in the general population. Microcephaly (head circumference >2SD below mean for age and gender) and is considered a surrogate for brain growth is reported in more than 30% in children with various types of CHD[35, 47]. The latter relates to the described altered intrauterine blood flow distribution and resistance in children with CHD. In absence of abnormal umbilical artery flow, third trimester fetuses with CHD have smaller head circumference[48] and decreased volumetric brain growth[49] than do normal fetuses. This is suggested to be caused by inadequate delivery of oxygen and metabolic substrate to the developing brain.

CHD is often accompanied with prematurity and/ or low birth weight (< 2500gr) in term CHD neonates[50], which may complicate treatment and encompass intrinsic risk factors for adverse long-term neurodevelopment[51].

3.1.3. Genetics

A substantial proportion of children with CHD has significant non-cardiac comorbidities, such as genetic polymorphisms or chromosomal structural abnormalities. Trisomy 21, Williams-Beuren syndrome, Noonan's syndrome, and 22q11.2 microdeletion (DiGeorge or velocardiofacial syndrome) all have a high rate of CHD[52]. When detected in children with CHD, genetic anomalies are identified as independent predictors for poor neurodevelopmental outcomes[20, 53].

Apolipoprotein E (ApoE), synthesized by the liver and brain, is a cholesterol regulator and important for neuronal repair and serves as an example of how gene-environment interactions affects susceptibility for neuronal injury. Genetic polymorphisms of this protein have been found to affect neuroresiliency and neurodevelopmental phenotypes in children who suffered lead exposure, oxygen deprivation, and cerebral palsy[54-56]. Variants of apolipoprotein E have also been studied as risk factors for poor neurodevelopmental outcome in children with CHD. In a longitudinal follow-up study, Gaynor and colleagues identified the ApoE allele ε2 as a significant and independent predictor for poor psychomotor functioning and adverse behavioral outcomes in a large cohort of children that had cardiac surgery with CPB at 6 months or less[47, 57, 58]. These findings reflect that certain

genotypes that do not cause CHD alter the response to environmental factors and decrease resiliency for neurological injury. Early genetic screening is key to provide a neurological and cognitive prognosis for the patient and his/her family in view of proper and early referral when necessary.

3.1.4. Age at intervention

Majnemer and colleagues prospectively followed a cohort of diverse CHD patients who were treated in the newborn (< 1 month of age) or the infant (between 1-24 months of age) period[27]. These groups showed a divergent neurodevelopmental pattern, with lower intelligence scores at school entry for patients who had cardiac surgery for acyanotic CHD at older age. Complex CHD necessitates urgent intervention, typically in the neonate period, to prevent the culminating effect of chronic hypoxia. Medical intervention of patients with mild CHD is regularly postponed because absence of critical condition. However, low systemic cardiac output due to acyanotic CHD, and extending until cardiac repair may enclose its own risks for abnormal cerebral perfusion[59]. Considering optimal timing for medical intervention for CHD that will minimize acute and chronic exposure to hypoxia-induced neurological events remains a significant focus of interest.

3.1.5. Preoperative oxygen saturation

Children presenting with respiratory distress and low oxygen saturation requiring preoperative intubation are at greater risk for poor mental functioning[20, 46]. Requiring preoperative intubation may also increase the risk of perioperative stroke[60], adding to the culminating effect of preoperative hypoxia.

3.1.6. The brain - heart of the matter

Heart and brain develop simultaneous in the human fetus and their development is based on a dynamic physiologic and morphogenetic interaction; prenatal neurologic structures are highly metabolic and depend on the heart for delivery of oxygen and nutrients, where the heart needs innervations and control from the autonomic nervous system, the latter is dependent for oxygen delivery of the first-mentioned. It is not surprising that the disruption in the development of one organ affects the other.

Most studies in the 1980's and 1990's on neurodevelopmental outcomes in CHD patients undergoing neonatal or infant cardiac surgery mainly focused on perioperative techniques that presumably hampered cerebral perfusion through application of CPB, resulting in neurological injury (EEG abnormalities). Accumulating evidence nowadays suggests that these children enter the operating room with compromised neurological development, due to hemodynamic circulatory alterations, adverse brain development and extended cerebral hypoperfusion that is prenatal in origin[49, 61], and causes increased vulnerability for hypoxic events.

Early postmortem studies in 40 HLH patients, half of whom did not undergo surgery, showed that 45% presented with a combination of hypoxic-ischemic lesions and neurologic hemorrhages[62]. Preoperative cranial ultrasound abnormalities have been documented in up to 59% in CHD populations, comprising of cerebral atrophy, linear echo densities in the basal ganglia or thalamus, intraventricular hemorrhage and periventricular and intraprenchymal echodensities[63]. Over the following years, studies identified preoperative brain abnormalities predominantly characterized by white matter injury consisting of periventricular leukomalacia (PVL, necrosis of deep white matter adjacent to the lateral ventricles), and infarctions[64-66]. Open operculum[65], as well as altered cortical folding[67] were documented prior to surgery using modern structural brain imaging techniques. These findings may reflect an underlying structural brain immaturity and subsequent proneness for hypoxic-ischemic induced neuronal damage[68].

In Mahle's study[65], the incidence of PVL as measured by brain MRI increased from 16% prior to surgery to 48% postoperatively, infarctions from 8% to 19% early postoperatively (5-12 days) for two-ventricle or single ventricle circulation in 24 term neonates. New parenchymal hemorrhage was seen in 33%. Similarly, another prospective study found that more than 30% of 62 newborns with CHD had diffuse brain injuries (white matter injury, stroke, and intraventricular hemorrhage) prior to surgery, new postoperative brain injury was documented in 35% of the cohort, with increased risk for patients requiring Norwood procedures[69].

A companion article concerning the hematocrit trials in Boston, identified in a subset of enrolled patients returning for follow-up at 1 year that subtle hemorrhagic foci throughout the cerebral cortex, white matter, basal ganglia, and cerebellum were predictive for a loss of 10 points in mean PDI scores on the BSID, while no effect was found for MDI scores[70]. At age 14 and typically attending secondary education, regional brain volume reduction, including lower grey and white matter volume, has been observed in CHD populations and is related to long term neurodevelopmental outcomes[71].

The clinical presentation of these preoperative brain abnormalities were reported by a Canadian series of studies evaluating outcomes after newborn (n=56) or infant (n=57) cardiac surgery for diverse diagnostic categories of CHD. In the first group, 50% presented with abnormal neurological evaluations, including hypotonia, hypertonia, jitteriness, motor asymmetry, and absent suck, behavioral state of consciousness regulation, and seizures. In the latter group, hypotonia, head preference (head consistently turned to one side), lethargy, restlessness and agitation, motor asymmetry constituted the abnormal neurological profile[22]. Postoperatively, the newborn group's neurologic status was remarkably similar to the first neurological examination; new postoperative neurologic findings included jitteriness, motor asymmetries, cranial nerve abnormalities and seizures and were seen in 25%. The infant group's postoperative neurologic examination results remained unchanged for the majority of the patients.

Only recently, brain injury in fetuses with CHD has been prospectively assessed by Brossard-Racine and co-workers[61]. Altered brain development was found in up to 23% of the afflicted unborn children, including mild unilateral ventriculomegaly and increased extra-axial cerebrospinal fluid extra-axial spaces, and were not significantly different among cyanotic or acyanotic CHD patients. Another line of thinking in adverse prenatal neurologic development considers differences in prenatal cerebrovascular resistance and cerebral flow that may underlie postnatal adverse neurodevelopmental outcome among single ventricle patients[72].

Overall, these findings suggest that there is an underlying neurological substrate that is susceptible to the oxygen-depleting effects of the cardiac disease

antenatal and/or early postnatal, and may be further compromised by perioperative events. In addition, these results support the notion that the neurologic development in CHD patients strongly resembles that of premature children and that delayed brain maturation is likely a direct consequence of the CHD diagnosis [68]. Brain imaging may provide early prognostic information related to long-term outcomes.

3.2. Surgical management and intraoperative factors

Congenital cardiac diseases, once deemed fatal, can now be adequately corrected or palliated through advances in pediatric cardiology, cardiothoracic surgery, and intensive/neonatal care. Symptomatic CHD conditions necessitate medical intervention early in life because of heart failure or persistent hypoxemia extending until cardiac repair. Where cyanotic conditions require open-heart surgery or staged palliative treatment procedures early in infancy, treatment for symptomatic acyanotic patients is mostly limited to a single cardiac surgery or transcatheter-guided intervention at a later age.

3.2.1. Intraoperative strategies and hemodynamics

Hypothermia is often applied in cardiac surgery. Reducing the core temperature of the body lowers the metabolic activity and systemic oxygen demand, and protects vital organs from ischemia induced injury, especially the brain[73]. The cerebral metabolic rate is merely 10% of that at normothermia when cooled to 18°C.

Deep hypothermia with total circulatory arrest (DHCA) and deep hypothermia with continuous low-flow cardiopulmonary bypass (LFBP), next to normothermic perfusion CPB are the major support techniques during pediatric cardiac surgery. Cardiopulmonary bypass incorporates a pump and a gas exchange device to substitute for the function of the heart and lungs during surgery, allowing surgeons to operate in a blood-free and controlled environment. When the nature of the condition or surgical procedure requires a complete cessation of blood flow, DHCA is applied. The profound cooling process, delivery of cardioplegia, with or without aortic cross-clamping enables the surgeon to perform a rapid and accurate repair in a bloodless and motionless field while minimizing the duration of CPB. This technique is applied on the premise that there is a safe duration of DHCA, which is inversely related to body temperature and determined by the susceptibility of the brain for neurological compromise[74]. However, the alternative

low-flow CPB, although maintaining continuous cerebral circulation, has its own pump-related sources of brain injury (emboli or inflammation through high levels of cytokines)[75].

Well-designed prospective randomized clinical trials have resulted in conflicting findings regarding the neurodevelopmental effects of intraoperative management strategy manipulation.

The most comprehensive data on the effects of surgical techniques on the vulnerable young brain were provided by the group at Boston Children's Hospital. Three prospective randomized trials were conducted to evaluate the manipulation effect of total circulatory arrest versus utilization of low-flow bypass, pH strategy, and optimal hematocrit on later neurodevelopmental outcomes[19, 76, 77]. When randomly assigned to DHCA, greater neurological morbidity was observed and included higher rates of postoperative clinical seizures, abnormal electroencephalogram (EEG) activity, and greater releases of creatinine kinase enzymes[74]. At one year, neurodevelopmental outcome was assessed in 155 of these 171 patients using the BSID. Outcomes showed that children assigned to surgery where DHCA was the main support method, obtained significantly lower scores on psychomotor tasks than the counterparts assigned to the low-flow CPB condition. Moreover, those subjected to a longer period of DHCA, with a ventricular septal defect, and displayed EEG seizure activity were at particular risk for poor performance[19]. Concurring with these results and regarding the concern of the effects of DHCA on the neonatal brain, some centers began to avoid the use of DHCA, in favor of continuous low flow CPB[78].

Follow-up at 4 and 8 years in the former cohort made clear that IQ scores, although in low-average ranges, and overall neurologic status were comparable among patient groups, thus the impact of DHCA became less clear. In terms of neuropsychology and academic functioning, patients assigned to DHCA performed poorer on motor skills, expressive language, and visual-motor tracking, while the other cohort displayed an impulsive task strategy and had behavioral problems [16, 25]. Surprisingly, social class and the presence of a VSD seemed to explain more of the variance in intelligence scores than did assignment to one of the intraoperative organ support methods (23.7%, 3.2%, and 0.3% respectively). A companion article described the additional risk of DHCA exceeding the threshold of 41 minutes to be associated with the reported adverse developmental

outcomes[79]. When reaching adolescence (mean age ~16), returning patients scored mostly in the low-average ranges on neurodevelopmental measures. Only marginal treatment group differences were apparent. The formerly defined predictor, early postoperative abnormal clinical or EEG seizures remained the factor most highly associated with adverse neurodevelopmental outcomes[38].

Optimal acid-base management during pediatric cardiac surgery has elicited great discussion on the utilization of α-stat or pH-stat strategy, since they differ in their approach to acid-base alteration that occurs with hypothermia[80].
In the first strategy, arterial gas samples are not corrected for temperature, resulting in increased alkalosis due to increased gas solubility and decreased partial pressure of carbon dioxide when body temperature drops. Although this strategy results in alkalosis, intracellular enzyme systems and preserved cerebral auto-regulation are mentioned as potential benefits of this pH management strategy. With the latter pH-stat strategy, carbon dioxide is added to the gas inflow of CPB circuits so that pH in arterial blood gas is corrected for temperature. This results in vasodilatation of cerebral blood vessels, facilitating the cooling process due to increased cerebral perfusion, but also has the potential to carry gaseous or particulate emboli to neurological structures. In the mid 1980's surgeons at Boston Children's Hospital began to change their pH approach to the more alkaline alpha-stat strategy based on comparative physiological animal studies, but after both laboratory and clinical studies using piglet models, the original pH-stat method seemed preferable[81]. Random assignment of 182 patients with various CHD (d-TGA, TOF/truncus arteriosus, VSD/CAVC) undergoing surgery at age less than 9 months, to one specific pH strategy resulted in a developmental profile at 1 year of age characterized by lower scores for d-TGA and TOF patients in the alpha-stat condition. In contrast, for patients with VSD/CAVC, mental developmental outcomes were significantly better when assigned to the alpha-stat strategy. Without controlling for diagnosis, overall neurodevelopmental outcomes in terms of psychomotor and developmental indexes did not differ significantly after randomizing infants to pH-stat or alpha-stat methods of pH management during pediatric cardiac surgery[82].

Hematocrit is the main determinant of the oxygen-carrying capacity of blood, and with CPB, hemodilution is inevitable through priming fluids in the CPB circuit.

Surgeons have argued about the optimal hematocrit level, with higher hematocrit resulting in improved oxygenation of tissue in contrast to lower levels leading to improved cerebral microcirculation due to decreased viscosity. Jonas et al.[77] aimed to study the optimal intraoperative hematocrit level in 147 infants undergoing cardiac surgery with CPB, with hematocrit at 20% or 30%. One-year assessment with the BSID showed less favourable outcomes for those assigned to lower hematocrit. Although MDI scores were similar between patient groups, the low-hematocrit patients had significantly lower PDI scores (81.9±15.7 vs 89.7±14.7) and 29% had PDI scores at least 2 standard deviations below the mean. In line of this work, hemodilution and its association with neurodevelopment was further explored. A companion article[83] showed that raising hematocrit levels to 25% or 35% had only marginal clinical benefits and no increased risk for poor neurodevelopmental outcome. A meta-analysis of both studies reported a non-linear relationship between PDI and hemodilution with improved scores at higher hematocrit (~24%) at onset of low flow CPB, followed by a plateau[84]. These results from a single center and well defined CHD population could not ascertain a universally "safe" hemodilution level.

The neurodevelopmental trajectory of patients treated for d-TGA assigned to a predominant support strategy of DHCA or LFBP during hypothermic CPB in an era without modern ultrafiltration, low hematocrit, and alpha-stat or pH-stat strategy seems to have its own developmental signature. The selective effects of DHCA were ultimately proven to be only modest.

3.2.2. Anterograde and retrograde regional cerebral perfusion

When the complexity of the CHD condition requires aortic arch reconstruction, surgeons may use DHCA or selective regional cerebral perfusion (RCP) methods. RCP was developed to eliminate or minimize the use of DHCA, since the reports of the Boston series suggested that after a cut point of 41 minutes, DHCA is associated with adverse neurologic sequelae. Through special cannulation procedures, global organ perfusion is assured, providing surgeons an adequate timeframe for aortic arch reconstruction in complex CHD repair. Early reports on the comparison of DHCA and RCP suggested that surgical treatment for HLH with predominantly DHCA or selective RCP resulted in comparable neurodevelopmental outcomes at 1 year[85]. Similarly, early school-age neurodevelopmental outcomes

for children undergoing phased palliation for single ventricle anatomy with randomization in these intraoperative organ support techniques corroborate the former findings in neurodevelopmental outcomes between groups at 1 or 5 years[86, 87]. Andropoulos[88] reported that neurodevelopmental outcomes of 57 children aged 1 year, treated for single or biventricular CHD with RCP, obtain scores that adhere to the population-based means, except for language and motor scores. The authors concluded that this technique provides a safe and effective strategy in supporting the brain during neonatal aortic arch reconstruction. Comparability and generalization of these results are questionable since cannulation techniques, RCP flow rates, and monitoring may vary greatly among pediatric cardiac centers, without the recognition of interindividual biological variability in CHD cohorts. Further research should strive to elucidate these mechanisms.

3.2.3. Anesthesia

Children differ from adults in that many vital organs, such as the brain, are in continuous development and prone to toxic agents and events eliciting hypoxic/ischemic events. Knowledge of neurotoxicity of anesthetic agents and their influence on the young brain is accumulating, affecting cerebral perfusion and causing hemodynamic alterations. Recently, it has been put forward that the anesthesia used in young children in order to tolerate surgical procedures is detrimental for neurocognitive development. Apoptotic neurodegeneration has been found in immature animals exposed to anesthetic procedures, causing long-term cognitive difficulties and soon the analogy was made towards young patients subject to surgical procedures in which anesthesia is required[89]. Research showed that children undergoing medical interventions and exposed to anesthesia before the age of 3, perform worse on tasks of receptive and expressive language, but also abstract reasoning proved suboptimal[90]. To what extent this association is due to the anesthesia, the surgical procedure, or the condition which underlies the need for surgery, is still unclear.

3.2.4. Other parameters

Other considered intraoperative factors assumed to affect outcome including the risk for cerebral emboli after release of aortic crossclamp[91], S-100B as a biomarker for cerebral injury[92], and cardiopulmonary resuscitation, implying a

period of decreased cerebral perfusion or hypoxemia[93], have not provided clear effects on neurodevelopmental outcomes yet.

Intraoperative strategies have received considerable attention and fueled ongoing research regarding long-term neurocognitive development after surgery for CHD. Long consecutive periods of CPB and circulatory arrest times during open heart surgery in infancy have been found to influence cognitive outcomes adversely[22, 34, 94], while other studies provided conflicting data regarding intraoperative organ support methods[45, 95]. The results from the Boston Trials have undoubtedly contributed to the evolution in surgical management of CHD, with CPB techniques and the application of DHCA in pediatric cardiac surgery. One has to keep in mind that these trials were conducted in the late 1980's and early 1990's, an era where surgical management included alpha-stat strategy, hemodilution with hematocrit maintained at 20%, no arterial filters, and outmoded CPB hardware were part of standard care. However, these trials provided us with a unique understanding of long-term neurodevelopmental outcomes after pediatric cardiac surgery for d-TGA using different support strategies. Awareness that these children are at risk for neurodevelopmental impairments has been rising among experts in the field ever since.

3.3. Postoperative variables

The immediate postoperative period in the pediatric intensive care unit is challenging for both patients and health care providers. Various clinical and biochemical parameters have to be monitored continuously to warrant optimal postoperative management. Some markers have proven to be associated with late cognitive outcome.

3.3.1. Hemodynamic stability

It has been demonstrated that high concentrations of lactate in arterial blood, a marker for tissue hypoxia, are a significant predictor for postoperative morbidity and mortality[96]. In contrast to studies in adult populations undergoing cardiac surgery, glucose measurements did not reveal a particular risk for early postoperative hyperglycemia on neurodevelopmental outcomes in children who had biventricular or univentricular repair of in infancy[97, 98].

3.3.2. Perioperative clinical and EEG-seizures

Seizures may manifest as a result from acute neurological injury after neonate surgery for CHD and are particularly prevalent in those with complex cardio-pathologies[99]. The early reports of the Boston studies already showed that postoperative EEG seizure activity was associated with worse outcomes[19]. Similarly, Gaynor reported that postoperative EEG seizures in children with complex CHD were associated with worse neurodevelopmental outcomes at 4 years of age[100]. Several studies have supported the high prevalence of this biomarker of brain injury on CHD populations[29, 94]. These findings warrant the adaption of standard continuous electroencephalographic seizure activity during the critical period in the intensive care unit.

Cardiac arrest, unsuccessful weaning from CPB, low cardiac output, or hypoxia may result in the deployment of *extracorporeal membrane oxygenation* (ECMO) as a life-sustaining measure. ECMO takes over the heart and lung function through blood gas exchange and membrane oxygenation. This vital organ support technique may have its own intrinsic risk factors for inflammatory responses and intracranial insults[101]. A prospective longitudinal Dutch study showed that adverse outcomes are common in children subjected to ECMO in infancy[102]. The authors found that in a cohort of 135 children diagnosed with meconium aspiration syndrome, congenital diaphragmatic hernia, and other conditions requiring this procedure that 9% attended special education or received extra support when following regular educational trajectories (39%). Parents and teachers reported more attentional, somatic, social, thought, aggressive and total behavior problems. Evidence for cognitive problems was found mainly in terms of working speed and concentration. In CHD cohorts supported with ECMO after cardiac surgery, suspect or abnormal neurodevelopmental outcomes were reported in up to 50%[103]. To what extent these outcomes are solely determined by the application of ECMO and which neurological structures are particular susceptible for injury remains to be determined.

3.3.3. Length of stay (in intensive care unit)

Prolonged hospital or intensive care unit (ICU) stay may serve as a surrogate marker for intensified postoperative monitoring, presumably due to adverse events in hemodynamics or neurological abnormalities. Many studies found that prolonged hospital or intensive care unit stay were independent predictors for poor neurodevelopmental functioning[20, 94]. Newburger and colleagues[104] reported that each day of cardiac intensive care unit (CICU) stay after surgical treatment for d-TGA accounted for a reduction of 1.4 points in full-scale IQ; 1.5 points in verbal IQ; 1.0 points in performance IQ; and 1.6 points in mathematics achievement at a mean age of 8 years. Furthermore, patients with a CICU stay of 8 days or more had a 7.4 point reduction in full scale IQ as compared to those CICU stay was restricted to a maximum of 4 days.

In addition, multiple hospitalizations for the management of CHD reflect a more complex medical course and are associated with both poor cognitive outcomes[20, 35], as well as more behavioral problems[105].

3.4. Other mediating factors

Over the years, other factors outside the hospital were found to contribute to long-term developmental outcome. Parental socio-economic status has received considerable attention in predicting adverse mental, cognitive and motor outcomes in this clinical population[20, 26, 34]. Higher parental social class may balance the described effects of risk factors and improve neurodevelopmental outcomes throughout childhood.

Furthermore, the importance of family dynamics becomes apparent since elevated levels of parental stress have been found to predict cognitive, emotional, and behavioral disturbances in CHD populations[27, 106]. Contemporary research highlights the importance of family processes and its influence on long-term developmental outcomes[107].

In conclusion, the exact aetiology of this long-term adverse neurodevelopmental course is to all appearances multifactorial and factors are likely to be strongly interrelated and add to the cumulative effect of adverse neurodevelopmental outcomes (Fig 4).

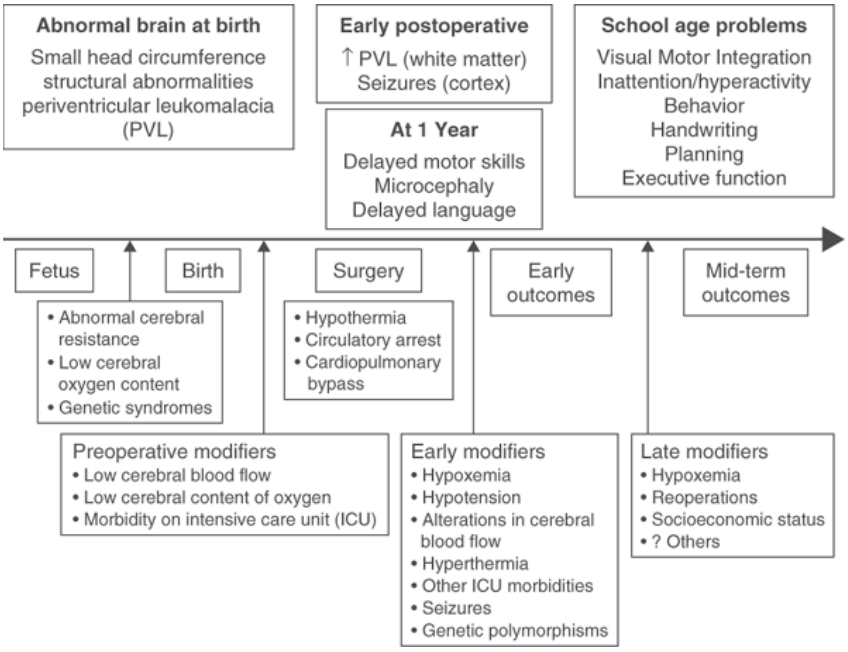

Fig 4. *Multiple factors which may adversely affect the central nervous system in children with complex congenital cardiac disease. Adapted from Wernovsky with permission of the publisher. Copyright © 2006, Cambridge University Press.*

Routine developmental testing is not implemented in the standard health care treatment program because of a lack in recognition that these children are at risk for neurodevelopmental delay or disability. Literature is often contradictory in the extent and spectrum of neurodevelopmental sequelae. With the growing number of survivors after treatment for (complex) CHD, better understanding of the neurobehavioral profile and its contributing factors is indispensable to maximize health care practice and optimize the child's developmental potential. To what extent the knowledge on adverse neurodevelopment in children treated for complex CHD is applicable to patients treated for mild and acyanotic CHD is still unclear. The major aim of this doctoral project was to identify neurobehavioral patterns in children treated for mild and complex CHD to increase awareness among health care practitioners, parents and teachers that these children may be at risk for developmental delay, and evaluate factors that might underpin this neurodevelopmental process. In this way, specific tailored interventions can be developed to support the child and their families coping with this condition.

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CHAPTER 2

OUTLINE OF THE STUDY

INTRODUCTION

The purpose and goal of this doctoral dissertation is to provide a better insight in the prevalence and processes involved in the adverse neurodevelopment of children treated for CHD. The current body of work stems from a multidisciplinary and multicenter study involving experts in fields of pediatric cardiology, pediatric and congenital cardiothoracic surgery, and developmental neuropsychology.

Instead of looking at neurodevelopmental outcomes of a group with a variety of CHD's, we choose to focus on specific diagnoses and its treatment. The neurobehavioral profile of patients treated for biventricular heart defects (BiVH) or univentricular physiology (UVH) became primary study goals. The BiVH group consisted of patients with an atrial or ventricular septal defect, treated with surgery or trans-catheter guided closure of the septal defect. The remaining subgroup comprised patients treated for UVH, hypoplastic left heart or tricuspid valve atresia, treated with staged palliative surgical interventions.

METHODS

Setting

Two specialized pediatric heart centers, Ghent University Hospital and University Hospital Gasthuisberg Leuven (Flanders, Belgium), and its Medical Ethics Committees gave consent to recruit and screen patients treated for CHD in early childhood.

Sample population

Patients

Patient files were retrieved and scanned for eligibility of patients in both pediatric cardiac institutions. BiVH patients were excluded if there was evidence for perinatal problems, preterm gestational age (<37 weeks), birth weight <2000gr, other cardiac malformations, genetic abnormalities or syndromes associated with developmental delay. UVH patients were only considered if they had no known or suspected genetic abnormalities, developmental syndromes or cerebral palsy.

Out of a 165 invited children, 96 parents/guardians of CHD patients responded positively to our appeal, a consent rate of 58%. This moderate consent rate reflects multiple challenges faced by this type of research. Causes for non-participation included diagnosis of developmental delay (5%), preterm birth (8%), family issues (2%) and no response at all (27%). Additionally, there were simultaneous ongoing

studies in the pediatric cardiac center in Leuven, competing for enrollment of the same group of patients, thus limiting the willingness of parents to participate. Eventually, our clinical population consisted of 79 patients who had BiVH repair and 17 UVH patients with staged palliation (Table 1).

Healthy control group

School boards of regular primary schools were contacted to participate and were requested to distribute a covering letter, a short survey on demographic characteristics (birth weight, - length, gestational age, Apgar scores, presence of a genetic disorder/ syndrome, parental occupational and educational level), and a consent form. Inclusion criteria were the same as for the patient group (birth weight > 2000g, without perinatal problems, without genetic abnormalities or developmental syndromes). After formal parental consent and validation of adequate matching with patient characteristics, these children were included in the study. All enrolled children attended school full time and did not experience any physical restrictions, nor had any developmental problems as reported by their parents.

Table 1. *Total patient group characteristics*

Variable	*Total patient group (N=96)*	*Total control group (N=96)*
Sex	♂:46 ♀:50	♂:46 ♀:50
Age at testing	9y1m ± 2y0m	9y1m ± 2y0m
Education mom (years)	13.8 ± 2.1	14.3 ± 2
Education dad (years)	13.3 ± 2.1	14 ± 2.6
Socioeconomic status	40.2 ± 8.1	42.3 ± 7.9
Birth weight, gr	3231 ± 503	3457 ± 576
Birth length, cm	49.3 ± 2.4	50.5 ± 2.6

Of the patient group, 66.7% was treated with open-heart surgery, 33.3% via transcatheter-guided repair (Tables 2-3). An univentricular heart condition such as hypoplastic left heart or tricuspid atresia was diagnosed in 17.7%. Two patients were excluded from further analysis because of transcatheter guided closure of a ventricular septal defect and avoiding possible confounds from this small group.
Surgical palliation or defect repair was performed in both groups according to diagnosis- and institution-specific protocols. The UVH group underwent staged surgical palliation between 2000-2009, initialized with the Norwood operation or pulmonary artery banding and concluded with the Fontan/Total Cavopulmonary Connection (TCPC) operation. In the HLH cohort, 6 of 8 patients had ante grade flow in their aortic arch prior to the Norwood procedure.

Patients with a BiVH defect were treated during 1999-2010 with one single open-heart surgery with mild-to-moderate hypothermic (25°C–37°C) cardiopulmonary bypass.

Table 2. *BiVH patient characteristics*

Variable	**VSD surgery (N=29)**			**ASD surgery (N=18)**			**ASD catheter (N=30)**		
Age intervention	0y6m	±	1y3m	2y8m	±	1y8m	4y2m	±	1y7m
Weight at intervention, kg	5.71	±	4	12.94	±	5.5	17	±	4.8
Defect size, mm	8.1	±	2.4	17	±	6	11.8	±	2.5
Hospital stay, days	10	±	5	6	±	2	2	±	0
ICU stay, days	3	±	4	2	±	1			
Duration surgery, min	160	±	89	118	±	35			
Duration ECC, min	77	±	48	43	±	22			
Duration aortic clamp time, min	45	±	35	28	±	17			
Duration anesthesia, min	268	±	107	209	±	48			
Duration intubation, min	2561	±	5066	807	±	1723			

Table 3. *UVH patient characteristics*

Variable	**HLH (N=8)**			**Tricuspid atresia (N=9)**		
Age intervention 1 (days)	18	±	15	35	±	30
Age intervention 2	0y6m	±	0y1m	0y8m	±	0y2m
Age intervention 3	2y7m	±	0y6m	3y5m	±	0y3m
Weight at intervention 1, kg	3.3	±	0.2	4.7	±	2.2
Weight at intervention 2, kg	7.1	±	1.5	8.7	±	2.3
Weight at intervention 3, kg	12.9	±	1.4	14.7	±	1.5
Hospital stay (lifetime – days)	45	±	16	38	±	17
ICU stay (lifetime – days)	10	±	8	12	±	8
Duration surgery (lifetime – minutes)	667	±	167	470	±	59
Duration ECC (lifetime – minutes)	280	±	70	160	±	38
Duration Clamp (lifetime – minutes)	97	±	43	53	±	28
Duration anesthesia (lifetime – minutes)	1019	±	182	741	±	107
Intubation Duration (lifetime – minutes)	9579	±	12365	7975	±	10898

To stratify risks for adverse neurodevelopment, we collected hospitalization data from medical files (with parental consent), suggested by contemporary literature to be related to long-term outcome (Table 4).

Table 4. *Medical variables collected from patient medical files*

Patient specific factors	*Gender, age at assessment, parental socio-economic status (as calculated by the Hollingshead Four Factor Index), pregnancy duration, Apgar score at 1 or 5 minutes after birth, birth weight and length, age and weight at moment of surgery, defect size (in septal defect patients)*
Preoperative factors	*S_aO_2 upon admission, lowest or mean arterial pressure, lowest pH, Hct, Hb, Cr, use of inotropic medication, use of prostaglandins, preoperative intubation*
Operative factors	*Number of surgeries, use of corticosteroid medication (methylprednisolone, prednisolone, dexamethasone, or hydrocortisone), cooling (lowest venous and arterial temperature, °C), mean operative arterial pressure, mean pH, mean PCO_2 , mean PO_2, mean S_aO_2, mean S_vO_2, mean Hb, mean glucose level, duration total surgery, duration aorta clamp, duration of ECC, duration of anesthesia, S_aO_2 immediately after CPB weaning*
Postoperative factors	*From first arterial blood sample in the morning or within 24h post-surgery: pH, PCO2, SaO2, Hb, Hct, Cr, lowest and highest recorded glycemia, glucose, lactate, CRP.* *Duration of mechanical ventilation, occurrence of clinical seizures, use of inotropic medication, SaO2 at hospital discharge (+screening for postoperative events via nurse notes), total ICU and hospital stay*

*Note: for those with complex CHD requiring staged palliation, data from all interventions (±3) were collected

Methods and materials

Intellectual and Neuropsychological assessment

Intelligence was evaluated using a shortened version of the *Wechsler Intelligence Scale for Children*, third edition, Dutch version (WISC-III-NL)[1]. In the short version of this general cognitive ability measurement, 2 verbal subtests (similarities and vocabulary) and 2 performance tasks (picture arrangement and block design) constitute a reliable measure of overall intelligence[2]. Estimates of full scale IQ is calculated by summing the subtask scores and compare these with the standard IQ conversion table. This abbreviated WISC-III has been shown to have good psychometric qualities and its reliability is set at .92[2].

The *NePsy-II-NL* (a Developmental Neuropsychological Assessment–2nd edition, Dutch version)[3] is a customizable test battery to assess an extensive range of neurocognitive skills in school-aged children. The Nepsy adapts the principles of the Lurian theory that states that higher cognitive functions are complex capacities composed of flexible and interactive subcomponents that are mediated by equally

flexible, interactive neural networks. Thus cognitive functions such as attention and executive functioning, language, learning and memory, sensory perception, motor function, and visuospatial abilities are mediated by multiple brain regions[4]. Children differ from adults in the way that not all subcomponents of a cognitive function are fully developed and specific cognitive tasks put more demand on the not yet fully developed neurologic network. Especially in terms of congenital or acquired neurologic abnormalities, modification in the functional development of different brain regions may occur. Impairment in one function will therefore affect other complex functions to which that subcomponent contributes in a way that an early occurring event may affect the chain of developmental processes. The NePsy permits a comprehensive review and evaluation of disorders of complex functions by assessing its subcomponents with specific tests. This allows the developmental neuropsychologist to assess basic, fundamental skills required to complete tasks that demand higher order cognitive processes. In this way primary deficits (e.g. deficient word decoding) that underpin secondary deficits (e.g. language problems) can be identified together with implications for other functional domains that include this subcomponent[3].

In a scientific statement of the American Heart Association, the NePsy was listed as a valid and reliable instrument to assess a variety of neuropsychological functions in children treated for CHD[5]. Domains of Attention and Executive Functioning, Language, Memory and Learning, Sensorimotor Integration, Social Perception, and Visuospatial Processing constitute the total neuropsychological battery used during this research project (Table 5).

Table 5. *Selected Nepsy tasks*

Nepsy domains	*Ability assessed*
Auditory Attention and Executive Functioning	
Auditory Attention and Response Test	Selective auditory attention; vigilance; shifting; inhibition
Design Fluency	Planning; problem solving skills
Inhibition	Shift and maintenance of new visual set; inhibition
Language Domain	
Comprehension of Instructions	Receiving, processing and executing oral instructions
Repetition of Nonsense Words	Phonological encoding and decoding
Speeded Naming	Rapid semantic access and production of names
Word Generation	Verbal productivity
Memory and Learning Domain	
Memory for Faces	Encoding of facial features; immediate and long-term memory for faces
Memory for Names	Name learning; short recall and long-term memory for names
Narrative Memory	Encoding of story details; free and cued recall
Word List Inference	Verbal working memory; repetition and recall after inference
Sensorimotor Domain	
Imitating Hand Positions	Visuospatial analysis and motor programming
Manual Motor Sequences	Imitation of rhythmic manual movement sequences
Fingertip Tapping	Rapid motor programming
Visuomotor Precision	Graphomotor speed; accuracy
Social Perception Domain	
Affect Recognition	Recognize and compare emotional affect
Theory of Mind	Ability to understand mental functions and another's point of view
Visuospatial Processing Domain	
Block Construction	Ability to reproduce 3D from 2D drawings
Design Copying	Motor and visuo-perceptual skills in copying 2D designs
Geometric Puzzles	Visuospatial analysis; mental rotation
Route Finding	Visuospatial relations; directionality

Behavioral functioning

Parents of all participants were asked to complete questionnaires on their child's cognitive, emotional and behavioral functioning.

The Achenbach Child Behavior Checklist. The Dutch version of the Achenbach Child Behavior Checklist for Children aged 6 to 18 (CBCL-6/18)[6] was completed by parents of each child to obtain standardized measures of various aspects of behavioral, social, and emotional functioning. These questions reveal information about eight scales that cluster into corresponding composite scales: internalizing behavior problems, externalizing behavior problems and total behavior problems. Also, 9 empirically derived scales were evaluated adhering to experts' based

Diagnostic and Statistical Manual of Mental Disorders (DSM) classification and allow stratifying the risk of psychopathology in clinical populations.

The Questionnaire on cognitive skills and emotional functioning was originally constructed by Newman et al.[7] to rate adult subjective complaints after coronary artery bypass surgery, and was adapted before in another similar study regarding cognitive functioning and emotional well-being of CHD patients as rated by parents[8]. The questionnaire includes 22 statements or questions regarding attention (sustained and divided), memory (recall and learning), problem solving strategies (planning and executing), and motor functioning (fine and gross motor skills). Items were rated on a four-point Likert scale (never – occasionally – mostly-always).

THESIS OUTLINE

Study hypotheses

Our study aims were two-fold. Firstly, we wanted to evaluate the neuropsychological and behavioral profile of children undergoing medical intervention (surgery or catheter based) for symptomatic acyanotic CHD since less attention has been given to this group with seemingly normal outcome. Secondly, we wanted to update the neurobehavioral profile of children undergoing phased surgical palliation for complex CHD. A common goal for the total patient cohort was to explore possible associations between various medical aspects and long-term neurodevelopmental and behavioral outcomes. The thesis outline below lists all studies adopted to evaluate these separate research goals.

Chapter 3 covers an exploratory study on the neurobehavioral outcomes of an acyanotic patient cohort treated surgically. A subgroup was selected from a larger database of patients with varieties of CHDs, investigated as a whole in a previous study[9]. Outcomes were compared to matched controls.

Analyses showed that, although intelligence scores were considered normal, these patients displayed problems in domains of attention, language, and fine motor skills. This conclusion was rather unexpected since acyanotic CHD's are considered relatively mild without additionally late morbidity. These unexpected results increased our interest in the neurobehavioral development of children treated for a relatively 'mild' CHD with current treatment protocols.

[Sarrechia, I, Miatton, M, et al. (2013). "Neurobehavioral functioning in school-aged children with a corrected septal heart defect." Acta Cardiologica 68(1): 23-30.]

Chapter 4 describes the neuropsychological and behavioral profile of children treated surgically for an atrial septal defect, secundum type (ASD-II) or a ventricular septum defect (VSD). Outcomes were compared with matched controls. This manuscript also explores associations between cognitive outcome and hospitalization data. Study hypothesis were that VSD patients, due to severe heart failure, longer procedural time, prolonged cross clamp time and hospital stay, would display more cognitive difficulties as compared to matched controls than the group of ASD-II treated surgically. Results showed that ASD-II patients were in disadvantage compared to controls in domains of attention, language, social cognition and visuospatial information processing, while VSD patients scored lower

on attentional skills and visuospatial information processing when compared to controls. Only few medical factors, but also socio-demographic factors were related to the neurocognitive outcomes.

[Sarrechia, I, Miatton, M, et al.(2015). "Neuropsychological outcome after surgery for acyanotic congenital heart disease." In Press – Research in Developmental Disabilities 2015; 45: 58-68*]*

Chapter 5 focuses on the neuropsychological profiles of children with corrected ASD-II and matched healthy controls. In addition, we evaluated the differential influence of treatment methods by comparing patients who underwent surgical closure and those who underwent catheter-based closure for ASD-II. We wanted to investigate if treatment with or without CPB techniques has a different impact on long-term neuropsychological development.

Compared with the matched controls, the whole ASD-II group scored lower on measures of attention, language, working memory, motor skills, social cognition and visuospatial skills. Comparing outcomes between surgical and the device cohort did not show a specific advantage of treatment. In terms of clinical relevance, the pattern of the scores show problems in inhibition, memory and visuospatial domains for surgically treated patients.

[Sarrechia, I, De Wolf, D, et al. (2015). "Neurodevelopment and behavior after transcatheter versus surgical closure of secundum type atrial septal defect." J Pediatr 166(1): 31-38.]

Chapter 6 contains an update concerning the neuropsychological profile of children treated for univentricular physiology with staged palliation. We hypothesize that there is a difference in neuropsychological outcomes in children treated for biventricular (BiVH) or univentricular heart (UVH) defects. This latter condition requires complex phased surgery to reconstruct normal circulation. In addition, we wanted to investigate if there is a difference in outcomes for children with hypoplastic left heart or children with tricuspid atresia, due to diminished preoperative cerebral perfusion or aortic surgery in the former cohort.

Statistical analyses indicated significant group differences between the UVH cohort and controls on domains of attention, fine motor skills, visuospatial abilities and to a lesser extent, memory performance. Parents of this clinical cohort reported more externalizing problem behavior and more school problems. The UVH group and the BiVH group did not differ on measures of neuropsychology or behavior.

[Sarrechia, I, Miatton, M, et al.(2015). "Neurocognitive development and behavior in school-aged children after surgery for univentricular or biventricular congenital heart disease." Eur J Cardiothorac Surg.]

Chapter 7 describes parental views on cognitive, emotional, and behavioral functioning in school-aged children treated for various CHD. Parents of patients were considered valid informants regarding these domains. We wanted to study the behavioral profile of CHD patients in general and evaluate whether the reported difficulties in earlier studies persist in the current epoch of highly specialized perioperative care.

Parents of patients reported significantly more problems on cognitive measures (attention, problem solving), motor functioning (fine and gross motor skills), and emotional problems (mood swings, anxiety). More internalizing problems were found in the patient group when compared to a healthy control group.

[Sarrechia, I, Miatton, M, et al. (2015). "Long-term behavioral and emotional outcomes in school-aged children following invasive treatment for congenital heart disease a multicenter experience."(Submitted)]

Finally, a concluding **Chapter 8** summarizes the main results of this dissertation and discusses limitations and future directions for research in this field.

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CHAPTER 3

NEUROBEHAVIORAL OUTCOMES IN SCHOOL-AGED CHILDREN WITH A CORRECTED SEPTAL HEART DEFECT

Sarrechia, I., Miatton M., De Wolf D., François K., & Vingerhoets G. *Neurobehavioral functioning in school-aged children with a corrected septal heart defect*. Acta Cardiologica, 2013. **68**(1): p. 23-30

ABSTRACT

Objective
This cross-sectional study assesses neurobehavioral consequences after surgical treatment for acyanotic congenital heart defect at the age of 5 to 12 years.

Methods
Fifteen school-aged children who underwent surgical intervention for a septal heart defect were examined with the short form Wechsler Intelligence Scale for Children-third Edition, Dutch Version (WISC-III-NL), and a neuropsychological assessment with the Nepsy. Performances were compared to a matched healthy control group. Parents completed the Child Behavior Checklist and were interviewed to rate the child's cognitive and emotional functioning. Children older than eight years filled out a self-perception questionnaire.

Results
Analyses revealed significant differences between the study groups on several cognitive and behavioral domains. Estimated intelligence scores were in the average range. Domains of attention and fine motor skills, and the subtest level of language abilities, elicited significant group differences, with less favourable outcomes for the patient group. Parents of patients reported more withdrawn behavior, social difficulties, thought problems, attentional shortcomings and lower competence for activities. These parents also indicated poor problem solving skills in everyday activities.

Conclusion
Surgical patients displayed subtle neuropsychological difficulties concerning language and fine motor skills. Behavioral difficulties were common. Future research should address risk factors for adverse neurobehavioral manifestations in this patient group.

Keywords
Neuropsychology • congenital heart defect • atrial septal defect • ventricular septal defect • neurobehavioral manifestations

INTRODUCTION

Acyanotic heart defects such as ventricular septal defects (VSD) and atrial septal defects type II (ASD-II) are among the most common forms of congenital heart disease (CHD) in Belgium representing respectively33% and 18% of children born with this affliction[1]. Relevant neurodevelopmental and cognitive comorbidity in corrected congenital heart disease children has been reported in numerous studies[2-6]. Despite average to low average intelligence[5-7], school-aged patients may deal with neuropsychological difficulties in areas of motor skills, perceptual organizational abilities, attention, information processing, memory and language development[7, 8], hampering academic achievement and future employment[9]. In addition, behavioral difficulties are regularly reported by parents of children who underwent invasive treatment for CHD, with internalizing and social problems being most prevalent[5, 10, 11]. Most studies suggests that children with acyanotic congenital heart disease, such as ASD or VSD, have a lower incidence of neuropsychological or developmental deficits than children suffering from a severe form such as Tetralogy of Fallot or the hypoplastic left heart syndrome[4, 12]. The former population might thus be easily overlooked and not considered at risk neither for developmental delays nor in need for adjusted support during childhood. There is only little evidence that children with CHD requiring surgery within the first month of life are at risk for neurobehavioral deficits appearing in the first year of life[13], and presenting with lower intellectual and cognitive capacities at school-age[5, 14].

The present study aims to provide a more comprehensive view on neuropsychological and behavioral functioning of school-aged children after correction of acyanotic CHD. This study also evaluated self-concept and cognitive skills in everyday activities (parent-report) in an attempt to specify a detailed psychological profile for this clinical population. The group was selected from a larger database of patients with a variety of congenital heart diseases, investigated as a whole in a previous study[7]. In this study, outcomes were compared with a matched control group of healthy peers.

METHODS

Participant characteristics and medical data

The CHD group consisted of 15 school-aged children (5 to 12 years) with acyanotic CHD: nine children with ASD and six with VSD. All children underwent corrective open heart surgery at Ghent University Hospital between August 1993 and September 2000 with full flow cardiopulmonary bypass under moderate hypothermia (25°C–32°C). Exclusion criteria were: birth weight of less than 2000g, important perinatal problems, non-cardiac malformations, or genetic abnormalities. All subjects were considered healthy at assessment. For all patients, a derived New York Heart Association classification was suggested by parents by means of indicating how the child copes with physical efforts. All patients were classified in the first category with no restrictions in physical activities and attending normal physical education classes at school. Family social class was estimated using the Hollingshead Four Factor Index, which combines parental occupational and educational level to compute a socioeconomic status score. Raw scores ranged from 13 to 56, with a higher score indicating a higher social status[15]. The control group consisted of 15 physically healthy children, recruited by means of contacting school boards and matched for sex, age and parental educational level.

The study was approved by the local ethics committee, all parents and children from the age of 12 gave written informed consent. Procedures were in accordance with the recommendations in the Helsinki Declaration of 1975[16].

Neuropsychological Assessment

Intelligence was examined with an abbreviated form of the Wechsler Intelligence Scale for Children- 3rd Edition, Dutch Version. This short form included two verbal tests (Information and Vocabulary) and two performance tests (Picture Completion and Block Design). An estimated intelligence quotient was calculated using the method of Sattler[17].

Neuropsychological performance was evaluated with all core subtests of the NePsy, NEuroPSYchological assessment[18]. The NePsy explores development in five functional domains (Attention and Executive functioning, Memory, Language, Visual-Spatial skills, and Sensorimotor functioning) to detect subtle deficiencies, which may interfere in learning in preschool and school-aged children. Domain scores were calculated.

Behavioral data

The Achenbach Child Behavior Checklist for Children aged 6 to 18 (CBCL-6/18) was used to obtain standardized measures of various aspects of behavioral, social and emotional functioning of the children as rated by their parents[19]. This questionnaire contains problem behavior scales and competence scales, to be rated in frequency on a Likert scale. The 113 items cluster into eight syndrome scales. Three composite scales are computed: Internalizing scale, Externalizing scale and grouped together, these scales constitute the Total Problem Behavior.

Each parent completed a semi-structured interview to assess one's perception of their child's cognitive functioning. This interview was adjusted to a paediatric population[20]. Parents answered 15 questions regarding attention (sustained and divided attention), memory functioning (recall and learning), problem solving strategies (task planning and executing), and motor skills (fine and gross motor abilities). Parents evaluated the frequency of this behavior (never, sometimes, mostly, always), with lower scores indicating fewer problem frequency. The median score was calculated to compute an overall domain score.

Child Self-Report

Children older than 8 years completed the Self Perception Profile for Children[21]. This scale assesses self-concept in 8- to 12-year-old children. Thirty-six items cluster in six scales that measure competence in school performance, social acceptance, athletic activities, physical appearance, moral behavior, and global self-worth.

Statistical Analysis

Demographics (age at assessment, gender and educational level of both parents), medical and birth characteristics (birth weight, birth length, Apgar scores and duration of stay in the intensive care unit) and outcome measures (Intelligence, neuropsychological outcomes, behavior, cognitive questionnaire, and self-perception) were compared between the CHD group and the healthy control group. Nominal data were analyzed with χ^2-statistics. We corrected for multiple testing using the False Discovery Rate[22].

Normality was checked with Kolmogorov-Smirnov tests. When criteria for normality were not reached, Mann Whitney-U-tests were used to explore group differences. For normally distributed data, a multivariate analysis of variance test

was carried out to investigate the neurobehavioral assessments with group (patient or control) as a between subject factor, the subtests of the intelligence scale and NePsy, both resulting in overall domain scores, were considered as dependent variables. Due to small sample size, a principal component analysis was not performed. Instead, the conventional structure of the NePsy was maintained to keep outcomes clinically relevant. Statistical significance was determined as p less than .05. Effect sizes were calculated to quantify the clinically meaningful differences between groups. Corrections and effect sizes were applied to domain scores and subtask scores separately. For parametric data, Cohen's d was computed (domain scores), for data that did not meet normality assumptions (sub task scores), effect sizes for Mann-Whitney, r, were calculated. Effect size was classified as small (d= .20/r=.10), moderate (d= .50/r= .30), large (d= .80/r=.50) and very large (d = 1.3/r= .70).

The Statistical Package for the Social Sciences: version 19 was used for all of the analyses.

RESULTS

Patient characteristics and medical data

The mean age at testing of the patient group was 8 years, 8 months. No group differences on demographic, medical or socioeconomic variables were found between the patient groups and they were considered as one group in further analysis. No significant differences emerged on any of the demographic variables between patients and controls. Demographics are presented in Table 1.

Neuropsychological Assessment

Mean unadjusted scores for each domain are listed in Table 2. The mean scores for all cognitive functions assessed were within one standard deviation of the mean, and are considered to be within normal ranges. General intelligence, measured with the short form WISC-III-NL, did not elicit group differences. Only the Vocabulary subtest revealed a significantly lower performance in the patient group (small effect size). Neuropsychological assessment showed that the clinical population had significantly lower achievements in the domains of *Attention and Executive* (moderate-to-large effect size) and *Sensorimotor* functioning (large effect size). On the subtest level, significant group differences emerged on Visual Attention, Phonological Processing, Comprehension of Instructions, and Imitating Hand

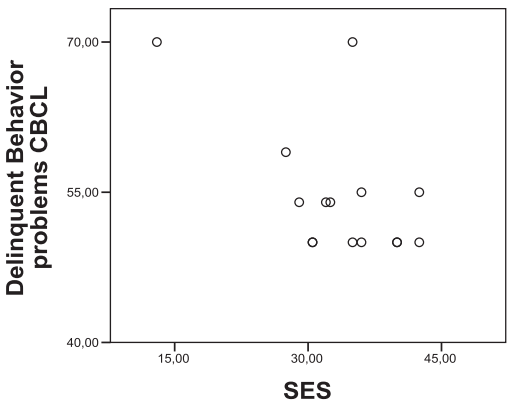
Positions, with less favourable outcomes for congenital heart disease children. Moderate-to large effect sizes were retained for these outcomes. Trends towards significant group differences were obtained for the subtests memory for Faces, Memory for Names, Speeded Naming, and the *Language* domain score. No other significant differences emerged.

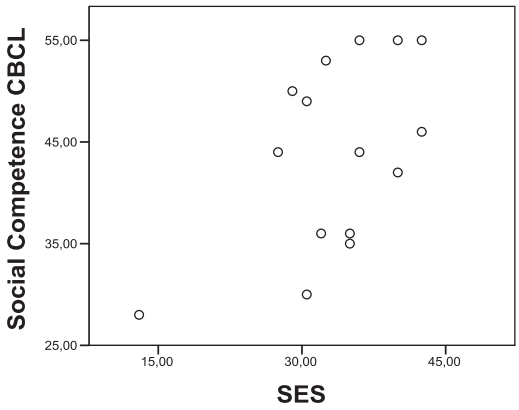
Multiple testing correction discarded some of these statistical significant findings, nevertheless we consider the clinically relevant findings of this study.

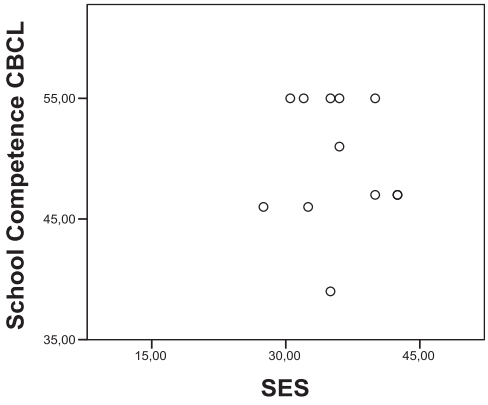
Behavioral functioning

Results are listed in Table 3.

Analysis showed significantly higher scores for the patient group on subscales of Withdrawn behavior, Social problems, Thought problems, and Attention problems, all accompanied by moderate to large effect sizes. A trend towards significant group differences emerged for the subscale Aggressive problem behavior, with higher perceived frequency in the patient group, with a small-to- moderate effect size. On competence level, parents of patients indicated significantly lower Activity competence, combined with a moderate-to-large effect size. Socioeconomic status in the patient group correlated significantly with the subscales delinquent behavior problems (r = -0.575, p = 0.025), social competence (r =0.538, p = 0.039) and school competence (r =0.588, p = 0.021). A number of parents of control children did not complete the questionnaire fully which resulted in a smaller group for these items (N= 13).







Although scatterplots for delinquent behavior and school competence are not that clear, the scatterplot for SES and social competence indicates a linear association.

Questionnaire on cognitive skills and the child's self-report

Parental perspective on cognitive skills of school-aged CHD-children only revealed difficulties in the domain of Memory. Moreover, parents of patients appeared to be good informants concerning the cognitive skills of their children since significant correlations were found between the NePsy domains and the scores of the cognitive semi-structured interview. The NePsy domain score on *Attention and Executive functioning* was significantly negatively correlated with the interview's domain score regarding attention ($r = -0.709$, $p = 0.003$). A significant negative relation existed between the NePsy *Memory* domain score and the memory items of the interview ($r = -0.630$, $p = 0.021$). No significant group differences emerged concerning self-perceived competence.

Table 1. *Patient characteristics and medical data*

Variable	ASD (n = 9)	VSD (n = 6)	PŁ	Patients (n = 15)	controls (n=15)	PŁ
Sex	3 ♂ 6 ♀	3 ♂ 3 ♀	.439‡	6 ♂ 9 ♀	6 ♂ 9 ♀	.273‡
Age at testing	8y5m±1y8m	9y 8m±1y2m	.135	8y 8m±1.6	8y11m±1y6m	.946
Birth weight (g)	3297 ± 732	3155 ± 560	.695	3240±650	3544 ± 638	.215
Birth length (cm)	49.1 ± 3.4	49.5 ± 2.2	.811	49.3 ± 2.9	50.5 ± 2.9	.262
	<4 :0%	<4 :0%		<4 :0%	<4: 6.7%	
Apgar at birth	4-6: 0%	4-6: 0%	1.00	4-6: 0%	4-6: 0%	.402‡
	7-10: 100%	7-10: 100%		7-10:100%	7-10: 93.3%	
Education father (y)	12.1 ± 1.3	14.3 ± 2.0	.050*¥	13.0 ±1.9	14 .1 ± 2.3	.202¥
Education mother (y)	12.8 ± 1.8	14.2 ± 2.5	.328¥	13.3 ±2.1	13.7 ± 2.0	.567¥
SES	30.5 ± 7.3	37.9 ± 5.3	.052	33.5 ±7.4	35.2 ± 9.8	.582
Age at operation	1y10m±1y3m	1y5m ± 1y9m	.649			
ICU stay (days)	1.2 ± 0.7	1.4 ± 0.5	.388¥			

Łdegrees of freedom = 1, ‡ χ^2 test, ¥Mann Whitney U-test, * p < .05

Table 2. *Mean performances, and standard deviations on IQ and NEPSY, F, and P value*

Variable	*Patient group 15*	*Control group 15*	*F/U* (df)	*p*	*Adj. p*	*Effect Size d/r*
INTELLIGENCE (M, SD)						
Estimated full scale IQ (100;15)	98 ± 16.6	106.2 ± 14.6	1.41	.259[a]	.345	.49
Picture completion (10;3)	8.1 ± 4.2	10.2 ± 3.5	2.06(27)	.163	.345	.26
Block Design (10;3)	9.9 ± 3.1	10.3 ± 3.2	.119(27)	.732	.732	.06
Information (10;3)	10.8 ± 3	11.4 ± 3	.239(27)	.629	.732	.06
Vocabulary (10;3)	9.9 ± 2	11.7 ± 2.3	5.06(27)	.033*	.165	.38
NEPSY						
Attention and Executive functioning (100;15)	113.1 ± 6.0	118.6 ± 9.8	3.15	.042[a]*	.076	.67
Tower (10;3)	13.3 ± 1.4	14.3 ± 2.1	1.94(28)	.175	.286	.25
Auditory Attention and Response set (10;3)	12.5 ± 1	11.7 ± 1.4	3.66(28)	.066	.141	.31
Visual Attention (10;3)	9.2 ± 2.5	11.2 ± 2.3	5.22(28)	.030*	.150	.37
Memory (100;15)	101.1 ± 16.3	109.3 ± 11.3	2.52	.061[a]	.076	.50
Memory for Faces (10;3)	9.5 ± 3.4	11.8 ± 2.2	4.14(25)	.053	.160	.34
Memory for Names (10;3)	9.0 ± 3.9	11.4 ± 2.2	4.01(25)	.056	.160	.32
Narrative Memory (10;3)	11.9 ± 2.9	11.3 ± 2.2	.413(25)	.526	.553	.09
Language (100;15)	102.3 ± 13.5	117.3 ± 15.8	2.58	.053	.076	1.11
Phonological processing (10;3)	11.1 ± 3.5	14.3 ± 2.2	8.74(28)	.006*	.046*	.46
Speeded Naming (10;3)	9.3 ± 2.7	11.3 ± 2.9	4.07(28)	.053	.160	.32
time (sec)	98.7 ± 35.7	82.5 ± 29.8	1.83(28)	.186	.286	.15
Errors	1.3 ± 1.8	0.3 ± 0.4	87.5(28)	.305¥	.403	.22
Comprehension of Instructions (10;3)	10.9 ± 2.2	12.9 ± 1.4	8.6(28)	.007*	.046*	.46
Visual-spatial Skills (100;15)	119.4 ± 9.9	120.3 ± 12.0	1.15	.330[a]	.330	.09
Design Copy (10;3)	15.3 ± 1.7	14.7 ± 1.9	.986(28)	.329	.403	.12
Arrows (10;3)	11 ± 1.9	11.9 ± 2.9	.929(28)	.343	.403	.16
Sensorimotor Functioning (100;15)	89.9 ± 14.5	102.5 ± 9.7	2.78	.041[a]*	.076	1.10
Imitating Hand Positions (10;3)	8.1 ± 2.7	11.1 ± 2.2	9.91(27)	.004*	.046*	.49
Fingertip Tapping (10;3)	9.7 ± 1.5	10.9 ± 1.9	3.55(27)	.070	.140	.33
Visuomotor Precision (10;3)	8.0 ± 3.2	9.2 ± 2.1	1.44(27)	.239	.341	.23
time (sec)	144.8 ± 66.9	145.3 ± 50.6	.001(27)	.980	.980	.06
Errors	12.5 ± 16.2	4.3 ± 6.2	3.36(27)	.078	.141	.30

[a] Multivariate test of subtests resulting in domain score, ¥ Mann-Whitney- U test, *significance level <.05
b Multiple testing correction according to the False Discovery Rate[22]

Table 3. *Behavioral functioning as measured by the CBCL completed by parents*

Problem behavior	Patient group 15		Controls 14				*Adj. p*	Effect size
	Mean ± SD	Freq>69 (%)b	Mean ± SD	Freq>69(%)b	F/U (df)	*p*		
Withdrawn	54.9 ± 6.2	6.7%	50.2 ± 0.8	0%	52.5 (27)	.020*¥	.068	.51
Physical complaints	55.9 ± 6.3	0%	54.6 ± 6.6	0%	.324 (27)	.574	.631	.11
Anxious/ depressed	56.2 ± 6.5	0%	53.1 ± 5.0	0%	73.5 (27)	.172¥	.270	.26
Social problems	55.7 ± 6.4	0%	52.1 ± 4.6	0%	58.0 (27)	.041*¥	.090	.40
Thought problems	54.4 ± 4.8	0%	50. ± 0	0%	49 (27)	.014*¥	.068	.58
Attention problems	61.9 ± 10.9	26.8%	54.2 ± 3.8	0%	6.31 (27)	.018*	.068	.28
Delinquent behavior	54.7 ± 6.8	13.3%	54.2 ± 3.3	0%	104.5 (27)	.983¥	.983	0
Aggressive behavior	58.5 ± 9.8	20.1%	52.8 ± 4.4	0%	4.02 (27)	.055	.100	.28
		Freq. > 63 (%)b		Freq. > 63 (%)b				
Internalizing	54.0 ± 10.3	6.7%	48.1 ± 8.3	0%	2.71 (27)	.066a	.109	.62
Externalizing	54.8 ± 11.3	26.8%	49.1 ± 8.8	7.1%	2.29 (27)	.121a	.161	.49
Total problem score	55.7 ± 12.7	26.8%	48.6 ± 10.4	0%	2.19 (27)	.073a	.109	.55
Competence scales	Patient group 15		Controls 14					
		Freq.<31 (%)c		Freq.<31 (%)c				
Activity	44.8 ± 9.1	6.7%	50.8 ± 7.8	7.7%	49.5	.025*¥	.068	.42
Social	43.9 ± 9.1	13.3%	47.3 ± 8.0	7.7%	1.10	.303	.370	.22
School	45.9 ± 9.4	13.3%	50.4 ± 7.0	0%	1.96	.173	.237	.25
Special education	Yes: 20% No: 80%		Yes: 0% No: 100%		3.12	.224‡		
Repeating school year	Yes: 20% No:80%		Yes: 0% No: 100%		2.91	.226‡		
School problems	Yes: 46.7% No:53.3%		Yes:15.4% No: 84.6%		3.12	.114‡		
		Freq.<37 (%)c		Freq.<37 (%)c				
Total competence	43.9 ± 13.1	26.8%	53.3 ± 11.3	7.7%	1.25	.312a	.312	.38

¥ Mann-Whitney- U test, ‡ χ^2 test (Fishers Exact test), a Multivariate test of subtests resulting in total problem behavior, b clinical significance is reached at t-scores >69 for subscales, at >63 for global scales, c clinical significance is reached at t-scores <31 for subscales, at <37 for the composite scale, *significance level <.05 b Multiple testing correction according to the False Discovery Rate[22]

DISCUSSION

Contemporary research on neuropsychological effects of paediatric cardiac surgical procedures mainly focused on cyanotic forms of CHD. This study highlights the importance of follow-up in a patient group rarely considered to be at risk for neurocognitive delay.

Neuropsychological performance

Intellectual capacities were found to be within normal ranges for both groups, thereby confirming other studies that explored intelligence in children with acyanotic CHD[6, 23].

Analysis of the neuropsychological battery scores revealed a significant difference in the domain of *Attention and Executive functioning* with a less favourable outcome for the clinical group, more specifically in terms of Visual Attention, suggesting poor speed and accuracy in arraying, locating, and distinguishing a target stimulus selectively. One of the few studies reporting on the neurobehavioral consequences after surgery for acyanotic CHD found a lower performance in young surgical patients on tasks of visual discrimination and sustained attention as compared to healthy non-surgical controls[14]. Visconti et al.[23] also reported restricted visual discrimination abilities in a group of surgical ASD patients. Sensorimotor functioning reveals poor Imitating Hand Positions in congenital heart disease children, indicating difficulty in visual-spatial analysis and motor programming. Deficient fine motor skills are frequently documented in children with CHD[3, 4, 7], and have been linked with perioperative events inducing neurologic injury[24].

Despite average-to-low-average performance, Language difficulties appear especially prominent in CHD patients with significantly lower Vocabulary scores on the intelligence scale indicating reduced word knowledge, and significantly lower performance in both productive (Phonological Processing) and receptive language abilities (Comprehension of Instructions). Poor phonemic awareness is an indicator of impaired auditory-phonological perception and analysis, which adversely affects receptive language abilities, spelling and learning[18]. This compromises the development of broader language skills and reading proficiency since phonological awareness underlies efficient reading decoding and spelling and is critical in linguistic skills[25]. Lower performance on Comprehension of Instructions indicates

poor processing and executing of verbal instructions of increasing syntactic complexity. Our results confirm the scarce previous reports on language difficulties in acyanotic patients[8, 26].

In the Memory domain trends towards significance were found on subtest level for Memory for Faces and Names, with a disadvantage for patients, indicating difficulties in adequate visual-spatial processing in the former subtest and problems with the efficient retrieval of visual-verbal associations in the latter which is suggested to be linked with deficits in linguistics in general[26].

Analysis revealed no significant group differences in the cohort for tasks on Visual-Spatial skills.

Results of the objective neuropsychological assessment match the subjective parental ratings, reflecting a fairly accurate parental view on their child's cognitive strengths and weaknesses, consistent with previous findings in this clinical cohort[20].

Although not statistically significant, a higher number of patient parents indicated more educational support and school problems. Three had repeated a school year, three required extra school services and parents of seven patients reported general school problems. In a larger sample size, this would probably result in a statistically significant difference. A study with a mixed CHD population pointed out that 9% of patients with atrial septal defect and 29% of patients with ventricular septal defect required special schooling and displayed limited academic achievement[9].

Behavior

Behavioral problems were common in the patient cohort as their parents indicated more Withdrawn behavior, Thought, Social and Attention problems as compared to healthy peers.

Though not statistically significant but worth mentioning is that 20% of the parents of patients reported Aggressive behavior within the clinical range, in agreement with findings of higher externalizing behavior problems (hyperactive, impulsive, or aggressive) in a similar patient population[14]. Competence in children with acyanotic CHD is found to be rated lower as compared to cyanotic CHD children[10], supporting our findings of lower Activity competence. Limitations in activities are less likely caused by increased fatigue and/or reduced physical activity since all patients attended normal physical education classes in school without

serious physical strains. Parents are concerned of the reserved behavior of their children leading to difficulties in socialization, whereupon they may be less motivated to engage in group activities or sports. Parents who have experienced life-threatening events with their infants may have difficulty in allowing their vulnerable children to participate in certain activities. Higher levels of parental stress have been found to influence intellectual development, cognitive abilities, behavior, and socialization skills[5]. Whether parents rated their child's behavior as more problematic due to their chronic condition, because they perceive their child as more vulnerable for problematic behavior, or take into account the affliction and do not rate the behavior as aberrant is unclear and gives rise to individual variability within the results.

Although there are verifiable subtle deficits in cognitive and behavioral areas in the patient cohort, this does not compromise the child's self-esteem, confirming findings of positive self-evaluations of children with different CHD-diagnoses[11]. It is possible that these positive self-evaluations reflect socially desirable answers as we found these descriptors contradictive to the obtained parental data on behavior and competence. One notion is that school-aged children may not have mastered their metacognitive knowledge yet and overrate school performance, social skills, and ethical behavior in general. This phenomenon is also described in children with ADHD as the Positive Illusory Bias; interplay between neurocognitive immaturity, ignorance of competence and the tendency to protect their self-image in self-perception, is plausible to give rise to this positive self-perception[27]. The group that completed the self-evaluation consisted of eight patients and nine healthy controls, and is thus rather small, so firm conclusions cannot be drawn.

Risk factors

Previous research on neuropsychological sequelae of invasive cardiovascular treatment in children mainly focused on surgical techniques thought to be responsible for cognitive dysfunctions in CHD populations[2, 28, 29].

Accumulating evidence suggests that underlying mechanisms for cognitive deficits are multifactorial, including preoperative, perioperative, postoperative factors as well as patient-specific characteristics[30]. Prior to surgical treatment, altered development in utero can be responsible for delayed prenatal neurological maturation and enhanced risk for acquired brain injury following cardiac interventions[31]. Limperopoulos et al.[13] postulated that acyanotic CHD patients are

more compromised in neurologic development than patients with cyanotic lesions by displaying more neurobehavioral abnormalities preoperatively. A left-to-right shunt causes prolonged poor systemic perfusion and enhances the risk of pulmonary hypertension and deficient cerebral blood flow preceding surgical procedures. The Boston Circulatory Arrest Trial set the trend in investigating the effect of perioperative procedures, such as deep hypothermic circulatory arrest and cardiopulmonary bypass techniques, on cognitive outcome[2, 3, 6, 23]. Although there remains controversy on adverse consequences of cardiopulmonary bypass on neuropsychological functioning in children after repair of acyanotic CHD[6, 23, 32], one study found a correlational trend for cardiopulmonary bypass in the first year of life and increased need for special schooling in congenital heart disease children[9].

Visconti et al.[23] reported that children who had surgery for ASD-II displayed lower intellectual capacities as compared to patients who had their septal defect closed through catheterization. It was argued that even brief periods of cardiopulmonary bypass, combined with the α-stat pH strategy, decreases hematocrit level, which is known to induce dilutional anemia and further compromises cerebral oxygen delivery[28]. Clearly, a distinct consensus has not been reached yet for minimizing risk factors and therefore optimizing long-term cognitive outcomes. Future research should address further elucidating of this complex interplay between possible causative factors.

In this small population sample no preoperative or long-term follow-up data were available, so longitudinal effects could not be studied. Generally, small sample size means smaller power, which requires cautious interpretation of the statistical data. On the other hand, our main findings are clearly in accordance with previous research, making the likelihood of statistical anomalies unlikely. Another study limitation is selection bias. Possibly only those parents, who observed neuropsychological or behavioral dysfunctioning in their child, may have responded to our appeal. Parental reactions on life threatening diseases of their offspring may result in clinical forms of overprotection, better known as the Vulnerable Child Syndrome[33]. Excessive parental concern and altered parent-child interaction can affect the child's cognitive, behavioral and socio-emotional development in a bidirectional way[5].

CONCLUSION

Intellectual, neuropsychological and behavioral assessment reveal that children who had surgery for acyanotic congenital heart disease are at risk for subtle cognitive dysfunction, confirming the scarce previous research[6, 14, 23]. Areas of visual attention, fine motor skills and language remain of particular concern and subclinical behavioral difficulties are common which ventures school performances, social skills and everyday activities at young age. It should be noted that, although our patient group scored significantly lower than the control group on several domains, they still scored within normal ranges and this does not always have clinical repercussions. By comparing objective neuropsychological functioning, parental view on behavior and cognitive skills, and self-perception, these results provide a comprehensive view on outcomes in school-aged children who had surgery for a septal heart defect.

Information on predictive factors for neuropsychological and behavioral functioning of children with a septal defect is of great importance to identify children at risk as early as possible. Moreover, parental reports during annual check-ups could be a valid predictor for early detection of developmental difficulties and would be indicative for clinical follow-up or treatment in patients with CHD. This way, clinicians, parents and teachers will be more attentive to cognitive and/or behavioral problems and suitable support regarding the child's individual needs can be recommended.

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CHAPTER 4

NEURODEVELOPMENTAL OUTCOME AFTER SURGERY FOR ACYANOTIC CONGENITAL HEART DISEASE

Sarrechia I., Miatton M., François K., Gewillig M., Meyns B., Vingerhoets G., & De Wolf D. *Neurodevelopmental outcome after surgery for acyanotic congenital heart disease*. In Press – Research in Developmental Disabilities 2015; **45**: 58-68

ABSTRACT

Objective
Inconsistent results on neuropsychological outcome in patients treated for acyanotic congenital heart disease (aCHD) questioned the clinical relevance of possible neurobehavioral sequelae in this group. This study was designed to objectify the neuropsychological profile and evaluate associations with medical data.

Methods
Patients with a corrected ventricular or atrial septal defect (n=46; mean age 9 years, 2 months) and a matched control group were submitted to evaluation of intelligence (Wechsler Intelligence Scale for Children, third edition, Dutch version) and screened with a neuropsychological test battery (a Developmental Neuropsychological Assessment, second edition, Dutch version). Hospitalization variables were retrieved to evaluate associations with cognitive outcome. Parents completed a behavioral checklist (Achenbach Child Behavior Checklist for Children aged 6-18).

Results
ASD-II patients showed lower scores in domains of visuospatial processing, language, attention, and social perception. VSD patients displayed subtle problems in attention and visuospatial information processing. Only few perioperative medical factors, but also socioeconomic variables were linked to cognitive outcomes. Parents of ASD-II patients reported more school problems when compared to controls.

Conclusion
After treatment for aCHD, subtle cognitive difficulties can present in domains of visuospatial information processing, language, attention, and social perception. These shortcomings might hamper school performances, as is suggested by lower school competence ratings. Ongoing follow-up and cognitive screening is warranted to promote developmental progress, in which both parents and clinicians share responsibility.

Keywords
Neuropsychology • congenital heart defect • atrial septal defect • ventricular septal defect • neurodevelopmental outcome

INTRODUCTION

Mortality in children with congenital heart disease (CHD) decreased substantially over the past decades. Hence, long-term morbidity, such as neurodevelopmental outcome and subsequent quality of life became more important in ongoing research. Acyanotic congenital heart defects (aCHD) such as atrial septal defect secundum type (ASD-II) or ventricular septal defect (VSD) are the most common congenital cardiac anomalies in children[1]. Although corrective procedures show excellent cardio-functional results, several studies reported on suboptimal neurobehavioral functioning for aCHD children in neuropsychological domains of attention, language, visuo-perceptual skills, motor functioning and social cognition[2-8], but findings in older aCHD patients show conflicting results[9]. This late cognitive morbidity may hinder academic attainment, employability, and ultimately associated quality of life when progressing into adulthood[10] .

Nowadays it is generally accepted that the etiology of neurocognitive sequelae after CHD repair is multifactorial with genetic, environmental, and perioperative management strategies all contributing to neurobehavioral outcome[11-13]. Moreover, neuroimaging methods such as Magnetic Resonance Imaging (MRI) and Diffusion Tensor Imaging (DTI) before and after surgery have been used to study atypical neurologic development caused by genetic etiology or hypoxic/ischemic events induced by the cardiac lesion[14]. These studies in turn revealed that reduced brain volumes in CHD patients are associated with functional cognitive outcomes[15].

We aimed to further elucidate the influence of possible medical and socio-economic correlates in long-term neurodevelopment for surgically treated congenital acyanotic cardio-pathology. Risk factors such as presence of genetic morbidity, duration of cardiopulmonary bypass (CPB), hospitalization, and cross-clamp time have been identified and studied numerous times for children with complex forms of CHD[8, 11, 12]. To what extent some of these factors influence the long-term development in school-aged children treated for mild CHD remains largely unknown. Majnemer et al.[8] identified acyanotic CHD as a particular risk factor for poor neurobehavioral in a longitudinal follow-up study.

This study's main objective was the description of the neuropsychological and behavioral outcome of children with a surgically corrected aCHD compared to matched healthy controls. Given that CPB techniques and cardioplegic arrest may

have a distinct impact at different ages, we expect divergent neuropsychological profiles in these patients. Moreover, due to heightened risk of volume overload, longer procedural time, prolonged cross clamp time and hospital stay, we hypothesized that VSD patients would show more subtle, yet significant cognitive difficulties as compared to matched controls than the group of surgically treated ASD-II patients. Medical parameters were retrieved from patient files to explore associations with long-term cognitive development.

In particular, we aimed to investigate whether the rising concern for developmental delays in aCHD children, rarely considered at risk, is warranted.

METHODS

Participants

Patients were recruited from 2 Belgian specialized pediatric heart centers, Ghent University Hospital and University Hospital Gasthuisberg Leuven. Patients with additional perinatal problems (asphyxia or infections such as toxoplasmosis, rubella or HIV), preterm gestational age (<37 weeks), birth weight of less than 2000gr, associated cardiac malformations, genetic abnormalities or developmental syndromes were excluded from the study.

Out of 83 invited patients, the parents of 46 (55%) responded positively to our call and these children were enrolled in the study. Reasons for non-participation included the presence of developmental delay (3%), refusal to participate (6%), and no response at all (36%). Responders and non-responders did not differ in age at intervention or total hospital stay. The clinical population consisted of 18 ASD-II surgery patients and 28 VSD surgery patients. All patients had corrective cardiac surgery with full flow cardiopulmonary bypass and mild to deep hypothermia (25°C–37°C) between 1999 and 2010. Neurodevelopmental testing was performed between the ages of 6 and 12. They were considered healthy at the moment of assessment and did not experience any physical restrictions as reported by their parents, whereupon a NYHA class of I was presumed (cardiac classes with no limitation of physical activity. The school-aged child takes gym class and keeps up with peers).

Healthy controls were recruited through approval of school boards of regular primary schools. We randomly contacted over 80 regular primary schools, of which 11 agreed to participate. We consulted school lists and selected children similar to our patients in terms of age, gender and educational level of parents (if provided).

Fifty families were approached and invited to participate, of which 46 responded positively (response rate 92%). These parents completed a short questionnaire on demographics and birth characteristics to affirm eligibility and after consent, these children were enrolled. The hospital's Medical Ethics Committees approved the study and parental written consent was obtained for all participants. Study protocol was in accordance with the Helsinki Declaration[16].

Materials

A shortened version of the WISC-III-NL (3rd edition, Dutch version) was adopted to obtain a valid and reliable estimate of overall intelligence[17].

A developmental neuropsychological battery (NePsy-II-NL; a Developmental Neuropsychological Assessment – 2nd edition, Dutch version)[18] was used to assess neurocognitive domains of Attention and Executive Functioning, Language, Memory and Learning, Sensorimotor Integration, Social Perception and Visuospatial Information Processing. Participants were assigned to 21 subtasks with 33 outcome scores targeting different aspects of the aforementioned domains.

Outcome scores were expressed as age-adjusted standardized scores (mean:10, SD:3), or percentile scores, which are considered to be process scores (pc<2–pc75). These scores assess specific abilities or error rates that enable the clinician to evaluate a child's performance in more detail.

Total test duration was three hours; breaks were provided during the test procedure to avoid fatigue. Parents completed demographic surveys. Meanwhile, socioeconomic status (SES) was estimated using the Hollingshead Four Factor Index, which combines parental occupational and educational level to compute a socioeconomic status score. Raw scores ranged from 27 to 66, with a higher score indicating higher social status.

All parents completed the Child Behavior Checklist (CBCL)[19]. This questionnaire contains problem behavior scales and competence scales, to be rated in frequency on a three-point Likert scale. The 113 items cluster into three composite scales: Internalizing scale, Externalizing scale and grouped together, these scales constitute the Total Problem Behavior.

Medical factors

Medical charts were retrieved for pre-, peri-, and post-operative data of the patients, to evaluate possible associations with cognitive outcome (Table 2).

Gender, SES age and weight at intervention were categorized as non-modifiable patient-specific parameters. Factors as duration of intensive care unit (ICU) stay, total hospital stay, surgery, time on extracorporeal circulation (ECC), clamp time, intubation, degree of cooling and several postoperative hemodynamic parameters and the first arterial blood sample in the morning post-surgery were considered (post)operative management parameters.

Data analysis

Normal distributed data are presented as means with standard deviation, non-normal distributed as medians with inter-quartile range, and clinical frequencies as indicated.

Nominal data were analyzed with Pearson's χ^2-statistics, or with Fisher's Exact Test. Since patients and controls were matched, paired t-tests and Wilcoxon matched-pairs signed ranks tests were rendered to explore group differences. We corrected for multiple testing by using the False Discovery Rate[20].

Effect sizes were calculated to quantify the clinically meaningful differences between groups. Corrections and effect sizes were applied to standardized scores and percentile scores separately. For parametric data, Cohen's d was computed, for data that did not meet normality assumptions, effect sizes for Wilcoxon signed-rank, r, were calculated. Effect size was classified as small (d= .20/r=.10), moderate (d= .50/r= .30), large (d= .80/r=.50) and very large (d = 1.3/r= .70). Spearman's Rho (two-tailed) explored associations between hospitalization variables and outcome measures.

The Statistical Package for the Social Sciences (SPSS) version 22 was used for statistical analyses. Statistical significance was reached at $p < .05$.

RESULTS

Patient characteristics and medical factors

Patient demographic data and medical parameters are listed in Table 1 and 2. Demographic characteristics did not differ significantly between the patient and control groups due to meticulous matching.

Neuropsychological assessment

Table 3 gives a comprehensive overview of the neuropsychological outcome of our study groups.

ASD-II vs. healthy controls

Analyses show that ASD-II patients performed worse compared to matched controls for several measures of intelligence. Estimated full-scale IQ was 15 points lower in ASD-II children (97.4 vs. 112.4, p=.010), which in IQ-psychometric terms is comparable to 1 SD. Effect sizes of all intelligence measures were in the moderate-to-large range (d= 0.45-1.08), indicating clinically meaningful differences between groups (Table 3).

Concerning neuropsychological performance, ASD-II patients scored significantly lower on 12 of 33 subtasks assessed, after multiple testing corrections. In eleven subtasks, the difference is clinically relevant, eliciting large to very large effect sizes (d ≥ 0.80).

ASD-II patients scored lower on a subtask of Attention, in Design Fluency, and they needed more time to inhibit a learned or automatic response in Inhibition-Time, the latter accompanied by a large to very large effect size (d=1.27). In the Language domain, lower scores were reported on subtasks Comprehension of Instructions and Repetition of Nonsense Words, and Word Generation (Semantic). Large to very large effect sizes in this domain indicate meaningful group differences (d ≥ 0.08). Evaluating Motor competency, difficulties in Imitating Hand Positions and the memorizing and executing Manual Motor Sequences are clear, both evoking moderate to large effect sizes (d ≥ 0.50). In the Social domain, Theory of Mind with Verbal and Contextual understanding of emotions yields significantly lower results in this patient group. Also in the same domain, a significant higher percentage of ASD-II patients scored in the clinical problematic range (≤pc 10) on the subtask of Affect Recognition (50% vs. 16.7%, p=.034), adhering the particular large effect sizes for both subtasks (d ≥ 0.80).

In the field of Visuospatial skills, children with ASD-II score lower on tasks of Block Construction and subtasks of Design Copying, the Motor component and the Local score. A higher proportion of these patients scored in the clinical range (>1SD below mean) for the Motor score in Design Copying (27.8% vs. 0%, p=.045), as well as for the Local score (33.3% vs. 0%, p=.019). Correspondingly, large effect sizes show meaningful group differences.

VSD vs. healthy controls

Children treated for VSD displayed similar intelligence scores compared to their matched healthy peers (105 vs. 105.5, *ns*), but scored lower on 3 of 33 selected NePsy tasks, of which 2 considered severe as indicated by large effect sizes (d ≥ 0.80). Paired analysis showed that patients needed significantly more time to complete an Inhibition task. Children treated for VSD obtained significantly lower scores for Visuospatial Skills Design Copying, on Motor and –Local assessment, with the latter resulting in a clinical meaningful difference (d ≥ 0.80). Moreover, a higher proportion of VSD patients scored in the clinical problematic range (≤ pc10) on the Total score of Design Copying compared to the matched controls (71.4% vs. 39.3%, p=.016).

Behavior

Analysis showed no significant difference between patients and controls on the subscales of the CBCL (Table 4). However, a statistically significant higher proportion of parent of ASD-II children reported school problems as compared to controls (33% vs. 0%).

Correlations

Next, we sought to determine the relation between medical parameters and neuropsychological variables that showed significant differences as compared to controls.

ASD-II

Several patient-specific factors disclosed associations with long-term cognitive outcomes. A positive relation existed between SES and performance on the Vocabulary scale (rs=.468, N=18, p=.05). Scores on Manual Motor Sequences were positively associated with age at intervention (rs=.492, N=18, p=.038) and weight at intervention (rs=.571, N=18, p=.013). Gender and defect size were not related to any of the outcome measures.

Correlation analysis with operative management parameters revealed that duration of hospitalization showed an inverse relation with performance of Manual Motor Sequences (rs=-.524, N=18, p=.026). Degree of cooling was negatively associated with language competence in Vocabulary (rs= -.553, N=18, p=.017) and Comprehension of Instructions (rs= -.492, N=18, p=.038). Operative pH levels were inversely related to Repetition of Nonsense Words (rs= -.546, N=18, p=.023), and with Theory of Mind subtask, the Verbal (rs=-.504, N=18, p=.033) and Contextual item (rs=-.532, N=18, p=.023).

Evaluation of postoperative parameters disclosed a positive association between highest glycemia levels and Total estimated IQ (rs=.668, N=17, p=.003) and Vocabulary (rs=.810, N=17, p=<.001), whereas lowest reported values of glycemia appeared associated with Total estimated IQ (rs=.594, N=17, p=.012), Vocabulary (rs=.618, N=17, p=.008), and Block Design (rs=.605, N=17, p=.010). Finally, postoperative mean lactate values were found to be inversely correlated with visuomotor and -spatial skills in Manual Motor Sequences (rs=-.494, N=18, p=.037) and Block Construction (rs=-.479, N=18, p=.044).

VSD

Examining relations with patient specific parameters of the VSD group revealed that scores on the visuospatial task of Design Copying-Local was inversely correlated with age at intervention (rs=-.400 N=28, p=.035) and weight at time of intervention (rs= -.427, N=28, p=.024).

Evaluation of medical factors revealed that preoperative creatinine was negatively associated with the subcomponents of Design Copying, the Motor score (rs=-.436, N=28, p=.020), and the Local score (rs=-.477, N=28, p=.010). Postoperative creatinine was also inversely related to the former mentioned outcome score (rs=-.477, N=28, p=.048).

Other perioperative parameters such as duration of surgery or total clamp time were not associated with cognitive outcomes. Postoperative hemodynamic markers such as or SaO2, hematocrit, hemoglobin or C-reactive protein levels did not reveal associations with long-term developmental outcome.

Table 1. *Demographics*

	ASD-II	ASD-II control	*p*	VSD	VSD control	*p*
N	18	18		28	28	
Sex	♂:6 ♀:12	♂:6♀:12	*1.0 χ^2*	♂:13 ♀:15	♂:13 ♀:15	*1.0 χ^2*
Mean test age	9y2m±2y2m	9y3m±2y2m	*.967*	8y9m±2y2m	9y0m±2y2m	*.951*
Birth weight (gr)	3430 (2953-3607)	3522 (3226-3967)	*.189*	3205 (2888-3622)	3320 (2902-3837)	*.384*
Birth length (cm)	49.5 (48.3-51.1)	50.0 (48.5-51)	*.724*	50 (48-51)	50 (48-51.5)	*.996*
Apgar score (1min), %	<4: 0 4-6: 13.3 7-10:86.7	<4: 0 4-6: 0 7-10: 100	*.492^E*	<4: 0 4-6: 0 7-10: 100	<4: 0 4-6: 5.9 7-10: 94.1	*.436^E*
Education mom (y)	12 (12-15)	15 (12-15.2)	*.225*	15 (12-15)	15 (12-15)	*.503*
Education dad (y)	12 (12-13.5)	12 (12-15)	*.134*	12 (12-15)	15 (12-15)	*.173*
SES	37 (33.5-41.2)	40 (36-47.5)	.091	40.5 (34.1-49)	42.1 (37-48.5)	*.780*

Data are presented as median (IQR) except for ages (mean ± SD)
For ASD-II patients, SES range was [28-50], for ASD-II controls [32-53], VSD patients [27-59], VSD controls [32-66]
χ^2(with Exact option)^E
**p<.05, **p<.01.*
Birth weight, length and Apgar scores were based on demographic reports provided by parents.

Table 2. *Patient characteristics*

Medical parameters	ASD-II	VSD	*p*
Mean age at intervention	2y8m±1y8m	0y6m±1y3m	<.001**
Weight intervention (pc), %	3-10:72.2 25-50:16.7 75-90:11.1	1-10:87.5 25-50:12.5 75-90:0	*.261*^{E}
Defect size (mm)	19 (14.25-21)	8 (7-10)	*<.001***
ICU stay (days)	1 (1-2.25)	3 (2-4)	*.001***
Hospital Stay (days)	7 (6-7)	8.5 (7-11.75)	*<.001***
Duration operation (min)	112.5 (95-131.2)	145 (110-175)	*.046**
Duration intubation (min)	350 (277-551)	1420 (705-1650)	*<.001***
Preop			
Creatinine (mg/dL)	0.51 (0.40-0.58)	0.49 (0.45-0.56)	*.916*
Hb (mg/dL)	12.3 (11.7-13.1)	11.2 (9.8-12.2)	*.001***
Periop			
Aorta cross clamp (min)	24 (15-36)	36 (29.5-57.5)	*.003***
Cooling (C°)	32 (31.5-36.25)	30 (28-32)	*<.001***
Mean arterial blood pressure (mmHg)	44.6 (39.9-49.7)	43.1 (39.1-50.4)	*.845*
Hb (g/dL)	8.25 (7.58-9.7)	8.6 (7.9-9.5)	*.543*
pH	7.34 (7.31-7.38)	7.34 (7.32-7.38)	*.676*
Postop			
SaO2(%)	98.9 (97.1-99)	98.8 (97.5-99.5)	*.355*
Creatinine (mg/dL)	0.48 (0.38-0.57)	0.54 (0.47-0.58)	*.053*
pH	7.39 (7.36-7.41)	7.39 (7.35-7.41)	*.803*
Glycemia High (mg/dL)	178 (138-224.5)	192 (166-262)	*.206*
Glycemia Low (mg/dL)	100 (91-109.5)	105 (85-130)	*.734*
Median mean lactate concentrations (mg/dL)	12.8 (9.7-18.3)	11 (9-13.2)	*.212*
CRP (mg/dL)	3.65 (2.32-5.04)	2.45 (1.6-4.42)	*.206*
Inotropic medication, %	Yes: 5.6 No: 94.4	Yes: 67.9 No:32.1	*<.001***^{E}

Data are presented as median (IQR), except for age (mean ± SD)
E *χ^2(with exact option)*
**p<.05, **p<.01.*

Table 3. *Neuropsychological performance in matched comparison*

	ASD-II	ASD-II control	p[a]	Effect size d/r	VSD	VSD control	*Adj. p*	Effect size d/r
N	18	18			28	28		
WISC-III-NL								
Full scale IQ	97±14.8	112±12.8	.010*	1.08	105±12.1	105±8.1	.954	0.04
Similarities	11.8±3.4	13.1±2.2	.212	0.45	12.3±2.3	11.6±2	.785	0.32
Picture arrangement	8.3±3.4	11.6±2.5	.010*	1.10	10.1±2.5	10.7±2.8	.785	0.22
Block Design	8.9±2.7	11.3±3.1	.027*	0.82	10.5±2.8	11±2	.785	0.20
Vocabulary	9.4±2	11.8±2.7	.015*	1.01	10.2±2.5	10.±1.9	.954	0
NEPSY								
Auditory Attention and Executive Functioning								
Auditory Attention(pc)	62(25-75)	75(75-75)	.075	0.41	75(56-75)	75(50-75)	1.0	0
Response Test(pc)	25(25-50)	50(43-50)	.245	0.26	50(25-50)	50(50-50)	.682	0.17
Inhibition error(pc)	25(21-75)	50(25-75)	.387	0.17	25(10-75)	25(10-75)	.898	0.08
Design Fluency	8.7±1.7	10.3±2.3	.018*	0.79	9.8±2.2	10.7±2.3	.348	0.40
Inhibition(pc)	50(50-62)	50(50-75)	.181	0.31	50(50-75)	50(50-75)	.573	0.21
Inhibition time	9.4±2	11.7±1.6	.004**	1.27	9.7±1.8	11.3±1.9	<.001**	0.86
Language Domain								
Comprehension of Instructions	9.8±2.7	13±1.8	.007**	1.39	11.3±2.8	11.1±2.1	.904	0.08
Repetition Nonsense Words	9.2±2.3	12.7±1.7	<.001**	1.73	10±2.3	11.7±2	.045*	0.78
Speeded Naming								
Total (pc)	25(25-50)	50(25-75)	.086	0.37	50(25-50)	50(25-50)	1.0	0.01
Time (pc)	75(75-75)	75(75-75)	.312	0.27	75(75-75)	75(75-75)	1.0	0.13
Word Generation								
Semantic	9±2.1	11.1±2.6	.026*	0.88	9.5±2.5	9.8±2.1	.834	0.13
Linguistic (pc)	25(7.5-62)	50(25-56)	.393	0.15	50(25-50)	50(10-50)	.845	0.10
Memory and Learning Domain								
Memory for Faces	9.6±3.3	10.1±2.6	*.908*	0.16	10±2.2	9.3±2.8	*.762*	0.27
Delayed	9.1±3.4	11.9±2.9	*.147*	0.88	11.4±3.5	11.4±2.7	*1.0*	0
Memory for Names	8.6±2.4	10.2±1.8	*.037**	0.75	9.3±2.6	9±2.6	*1.0*	0.11
Narrative Memory	10.4±2.3	11.4±1.8	*.241*	0.48	11.3±1.9	10.7±1.8	*.309*	0.32
Cued recall (pc)	50(25-50)	62(50-75)	*.075*	0.41	50(50-75)	50(50-75)	*.780*	0.13
Word List Inference								
Working memory	10.4±2	11.9±1.8	*.084*	0.78	10.1±1.8	10.3±1.9	*.904*	0.10
Word recall	11.1±2.5	12±2.4	*.186*	0.36	11.4±2.3	11±2.3	*.762*	0.17
Sensorimotor Domain								
Imitating Hand Positions	8.8±2.4	10.4±2	*.018**	0.72	9.4±2.6	10.2±1.8	*.355*	0.35
Manual Sequences	10.7±3.8	13.3±2.3	*.044**	0.82	11.8±2.8	12.8±1.9	*.349*	0.41
Visuomotor Precision(pc)								
Time (pc)	50(25-56)	50(50-75)	*.181*	0.30	50(25-75)	50(50-75)	*.898*	0.06
Error (pc)	50(19-75)	25(10-75)	*.531*	0.11	25(10-50)	25(13-75)	*.573*	0.17

Social Perception Domain								
Affect Recognition(pc)	17(4-56)	37(25-56)	*.235*	0.24	17 (2-50)	17(5-50)	*.573*	0.20
Theory of Mind								
Verbal	10±2.6	12.2±2.2	*.019**	0.91	10.9±2.7	11.1±2.1	*.904*	0.08
Contextual	9.1±2.4	11.3±1.6	*.015**	1.07	10.4±2.5	10.5±1.9	*.904*	0.04
Visuospatial Processing Domain								
Block Construction	9.3±1.9	12.8±2.4	*<.001***	1.61	11±2.2	11.6±2.4	*.762*	0.26
Design Copying (pc)	5(2-13.7)	10(10-25)	*.075*	0.40	10(5-25)	25(10-25)	*.105*	0.35
Motor	7.9±3.2	11.7±2.4	*.004***	1.34	10±2.5	11.8±2.3	*.006***	0.74
Global(pc)	25(10-50)	25(21-50)	*.181*	0.28	25(10-50)	25(25-50)	*.898*	0.07
Local	7.5±2.4	9.7±2	*.019**	0.99	8±2	9.7±1.8	*.006***	0.89
Geometric Puzzles (pc)	25(21-50)	50(25-56)	.181	0.30	50(25-50)	50(25-50)	1.0	0
Route Finding(pc)	25(10-25)	25(25-50)	.117	0.36	25(25-43)	25(25-50)	.127	0.31

Standardized scores (mean ± SD): Paired samples t-test
Pc scores (median (IQR), Wilcoxon Matched-Pairs Signed-Ranks Test.
p Adjusted: p-value according to the Benjamini- and Hochberg False Discovery Rate (1995).
Level of significance *p<.05, **p<.01.

Table 4. *Child Behavior Checklist*

CBCL	ASD-II	ASD-II-control	p	Effect size	VSD	VSD-control	*Adj. p*	Effect size
Internalizing	49.5±9.8	49.2±7.7	.909	.03	55±9	50±10.6	.184	.50
Externalizing	46.1±10.3	48.2±10.2	.459	.20	50.9±8.9	48.2±10.7	.503	.27
Total problem	48.8±10	47.3±7.6	.614	.16	53.8±8	49.7±10.3	.238	.44
Total competence	42.5±8.4	44.8±8.8	.453	.26	42.2±8.5	41.7±7.7	.531	.06
Special education,%	Yes: 5.6	Yes:0	1.0^{E}		Yes:10.7	Yes: 0	$.238^{E}$	
Repeating a school year,%	Yes: 22.2	Yes:0	$.104^{E}$		Yes:7.1	Yes: 4	1.0^{E}	
School problems,%	Yes: 33.3	Yes:0	$.019^{E}$*		Yes:32.1	Yes:20	$.317\chi^2$	

E χ^2(with Exact option)
*p<.05
p Adjusted: p-value according to the Benjamini- and Hochberg False Discovery Rate (1995).

DISCUSSION

Few studies have characterized the neuropsychological profile of children treated surgically for aCHD across all cognitive domains with a single standardized test battery. Our data provide a comprehensive outline of neuropsychological performance in ASD-II and VSD patients. Neurocognitive functions were assessed at school-age and compared with matched samples of healthy peers. Furthermore, outcomes were correlated with retrospectively collected perioperative variables and socioeconomic factors.

Neuropsychological profile

Overall, we see a fair performance of our clinical groups with mean scores within normal average ranges.

Remarkably, and contrary to our assumptions, the ASD-II patients (and not the surgical VSD patients) displayed lower scores in several domains when compared to controls. Children treated surgically for ASD-II displayed a 15-point difference in estimated full scale IQ. These results are in line with previous studies in children with various forms CHD where lower intelligence scores in acyanotic cohorts were evident[2, 3, 8].

Neuropsychologically, ASD-II and VSD patients needed more time to complete a naming task for inhibition skills as compared to their matched controls, suggesting difficulty with inhibiting a former learned or automatic response. The presence of attention difficulties have been demonstrated in similar cohorts of surgically treated aCHD patients[2, 4]. This may place children at risk for learning difficulties considering that attention and vigilance is essential for higher neurocognitive tasks these children face in everyday school life.

Similar to previous findings from our institution with a different patient sample[4], language difficulties were evident in our acyanotic cohort, confirming poor skills in both productive and receptive language. The ASD-II patients showed more difficulties in receiving, processing and executing oral instructions with increasing complexity. They also performed worse on word productivity, phonological encoding and decoding in the repetition of non-sense words. In accordance with the published results of Hövels-Gürich and colleagues on the high incidence of speech therapy and articulation problems in children with surgically corrected VSD[21], VSD patients in the current cohort demonstrated poor performance on repeating non-sense words, reflecting inadequate en- and decoding of words, but also lower

orofacial praxis and articulation abilities. Linguistic skills have been found to be suboptimal in children with CHD, placing them at risk for learning difficulties and delays in school functioning. Miatton et al.[22] documented problems in language scores in a school-aged cyanotic and acyanotic patient cohort.

The ASD-II patients in our study performed worse on tasks measuring ability to imitate finger and hand positions and to repeat a sequence of hand movements with varying complexity, suggesting inadequate tactile-kinesthetic feedback and poor eye-hand coordination. Reduced fine and gross motor skills are a robust finding in outcome studies in children with CHD[5, 6, 11, 23] and may impact overall physical and psychosocial well-being.

Affected motor skills have also been identified in cohorts treated for aCHD[6, 8, 22], suggesting that these children, may cope with an underlying neurological vulnerability before, during or after surgical repair. Another possibility is that parents adopt an overprotective parenting style following diagnosis and treatment that prevents these children from engaging in sports activities or other social activities requiring physical efforts. The exact origin of these persisting shortcomings in motor functioning has yet to be determined.

Our results show that children with corrected ASD-II performed poor on the contextual task of Theory of Mind, suggesting difficulties with perspective taking and with understanding contextual emotions. In addition, a significant proportion of these children scored in clinical problematic ranges on the subtask of Affect Recognition. Social cognition is an infrequent studied dimension in children with CHD, aside from parental reports[24, 25].

Communication impairments in 3-year-old children with mild to moderate CHD have been found25, and social cognition problems seem to persist into adolescence in cyanotic CHD cohorts[26].

Recently, direct evidence has been found for poor emotion comprehension in patients with corrected transpositions of the great arteries (TGA)[27]. Although aforementioned studies show that children, as well as adults with cyanotic CHD are at higher risk for deficits in social cognition, the results from the current study suggest that this domain deserves further attention in aCHD populations too.

Results show that the ASD-II patients score lower on visuospatial skills, specifically in converting and building 3D constructions, but also tend to score lower

than controls in visuo-perceptual analysis and understanding directionality. Significant higher percentages of ASD and VSD patients obtained results in clinical problematic ranges on subtasks of Design Copying as compared to healthy peers. Persisting poor hand-eye coordination and poor visuospatial information processing have been consistently found in cyanotic as well as acyanotic patient populations[3, 22].

Simons and colleagues demonstrated visual-motor integration to be poorer in patients operated for VSD when examined with the drawing test of the Wide Range Assessment of Visual-Motor abilities at a mean age of ~9 years[7]. The authors hypothesized that age at intervention may play an important role, as surgery at younger age may have detrimental effects on visual, non-verbal abilities.

This is in contrast with the results of the current study since age at intervention was inversely related to visuo-spatial information processing. Another study suggested that the deficient integration and coordination in visuospatial assessment is likely to be caused by impaired visuo-perceptual organization abilities in TGA patients, rather than problems in motor control or deficient meta-cognitive abilities[28], and might serve as an explanation for this clinical cohort too. Longitudinal follow-up studies should provide more information that could affect optimal timing for surgical intervention, assess determinants of these adverse outcomes in this domain, and temporal trends.

When reaching adulthood, these children may come to face different challenges next to academic attainment, such as employability. To what extent adverse neurodevelopmental outcomes at school-age will affect career opportunities, remains to be clarified by prospective longitudinal study designs. Previous research showed that grown-ups with congenital heart disease (GUCH) are disadvantaged on the job market when compared to peers[29]. Loup et al.'s results showed that disability pensions were more frequent in a group of patients treated for VSD[30]. These findings suggest that continuous follow-up, care and career coaching is warranted from childhood throughout adulthood in this cohort with seemingly normal outcome.

Behavior

A significant proportion of parents reported that their child treated surgically for ASD-II experienced school problems as compared to parental ratings of controls. This is in line with the neuropsychological performances they displayed. Further, VSD patients did not differ from matched controls in terms of behavioral outcome.

Associations with clinical and demographic variables for aCHD

Higher levels of postoperative glycemia and high SES were associated with better outcomes in the Intelligence domain for the ASD-II group. Linguistic scores were also found to be associated with SES and degree of cooling, underscoring the neuroprotective nature of cooling strategies. Visuospatial proficiency was associated with postoperative lactate levels, a marker for tissue hypoxia. It seems important to note that some intra-operative management factors classically associated with lower cognitive performance, such as duration of ECC, cross clamp time, metabolic acidosis (pH < 7.15), and long postoperative intubation period[12] did not result in significant correlations in this study.

On the other hand, this study contributes to the growing evidence that non-modifiable patient-specific factors such as SES are important determinants for later neurodevelopmental functioning[23, 31]. In a former study with aCHD patients, Quartermain and colleagues[9] assessed various neuropsychological skills pre- and postoperatively and explored associations with CPB procedures. No cognitive decline or independent effects of CPB and surgery could be identified except for one test of executive function, and this finding was considered a statistical artefact. The surgical CPB patients in the aforementioned study were treated at a mean age of 11.8 years (range 5 to 18 years); these patients might have been relatively longer symptom-free compared to our clinical cohort treated at a mean age of 0 to 3 (Table 2). Moreover, brain development and the response of the brain to CPB and cardioplegic arrest can have a varying impact at different ages. To what extent patient-specific and modifiable factors contribute to these specific adverse neuropsychological outcomes for this clinical group remains to be determined. As compared to normally developing children, many factors may affect the brain development and subsequent later higher cognitive functions of young children with aCHD.

Possibly, the adverse hemodynamic burden that patients with significant ASD-II suffer is underestimated in the current treatment protocol. Persistent hemodynamic instability in left-to-right shunting in the neonate leads to diminished systemic cardiac output, cardiovascular insufficiency and cause subtle cerebral ischemic damage. As a possible consequence, newborns with aCHD have been described to display high rates of neurologic abnormalities prior to surgery[8]. This might increase neurological vulnerability for intraoperative events.

Medical management of congenital heart defects often necessitates open heart surgery with the risk of air entrainment and emboli through manipulation of the heart or aorta. Evidence exists that microemboli in the carotid artery during pediatric cardiac surgery are particular prevalent after release of aortic crossclamp, even in 'low risk' ASD repair and independent of CPB duration[32]. Potentially, these microemboli may cause subtle hypoxic ischemic events and result in mild cognitive impairments at school-age. Intensified multimodal neurological monitoring with techniques as near-infrared cerebral oximetry, transcranial Doppler ultrasound, and electroencephalographic monitors may improve neurological outcomes and prevent adverse neurologic sequelae[33], even in 'low risk' pediatric populations. Postoperative complications in ASD-II patients are common and include mostly pericardial effusion and cardiac arrhythmias[34], prolonging their total hospital stay, a known risk factor associated with adverse neurodevelopment[5, 8].

In addition, knowledge on the relation between cognition, brain development and CHD is accumulating. The coexistence of CHD and abnormal brain maturation has been described in patients treated for aCHD without overt neurologic problem and imply reduced cortical grey matter volume, cerebellum, basal ganglia and hippocampus. These regions are related to intellectual functioning, perceptual reasoning and motor abilities[15], and may help to clarify the results in this study together with the socioeconomic effects.

Limitations

Typically in this type of research, we are faced with the possibility of selection bias. Only parents of children who indeed noticed neurocognitive difficulties might have responded to our appeal. This could be an alternative explanation for the lower performances in our ASD-II surgery group.

Although we did not receive any socio-demographic data from non-responders, the SES-score range is considered representative for the general population. It

should be noted that mean neurodevelopmental scores for the ASD control group fell in the average / high-average range, whereas the mean scores for the ASD-II patient group fell mostly within one standard deviation from the population-based mean and reflect mild weaknesses rather than significant impairments.

Preoperative screening in our patients was not conducted, so mild cognitive deficits might have been present before surgery. Although children with known genetic syndromes were excluded from our study sample, formal genetic screening was not always performed if there was no clinical indication. Statistical analyses and multivariate regression techniques were restricted and underpowered by the small sample size. Enrolling more control subjects (3:1 patient) to enhance statistical power might have enhanced the generalizability of the findings in this study.

We acknowledge that the medical variables studied are likely interrelated and therefore, we cannot proceed to evaluate the unique contribution of specific medical aspects in the management of aCHD. The retrospective nature of the study did not allow us to control for confounding variables that might have been present before surgery or neurodevelopmental testing. Nevertheless, our data suggest that, despite excellent functional septal defect repair, ASD-II and VSD patients are at risk for suboptimal neuropsychological outcomes which may hamper long-term school competence.

CONCLUSION

Limited up-to-date literature exists on the long-term neurodevelopment of children with corrected aCHD. Results in the current study suggest that patients treated for aCHD perform relatively well as a group when compared to healthy controls, but there remain some areas of concern, especially for patients treated for ASD-II. Neuropsychological problems emerge in domains of visuospatial information processing, language, attention, and social perception. Some hospitalization parameters, but also patient-specific factors were associated with these suboptimal outcomes.

We conclude that this study documents subtle neuropsychological impairments in school-aged children operated for aCHD with an uncomplicated clinical course. It seems advisable for clinicians to survey parents on the child's school functioning during follow-up visits to identify and refer those patients at risk. Recommendations relating to medical and developmental surveillance, screening and periodic re-

evaluation for children treated for CHD at risk for developmental delay have been outlined by the American Heart Association (AHA) and American Academy of Pediatrics (AAP)[35]. Neonates or newborns requiring open heart surgery are considered to be at risk for diffuse global developmental delay that has time phased variations and implications. The provided guidelines help to identify and treat those patients at risk and coordinate the multifaceted treatment process consisting of special education, behavioral counseling, speech/language, occupational and physical therapies to improve consistency in developmental follow-up across time. Taken together, this will guide cardiologists and health practitioners towards increased awareness and better understanding of neuropsychological sequelae after treatment for aCHD. Disentangling the multifactorial etiology that places some patient groups particularly at risk for adverse cognitive outcomes is very challenging. Prospective, multidisciplinary studies will yield more insight into the contributing factors concerning cognitive outcome and will allow improved prognosis in these children.

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CHAPTER 5
NEURODEVELOPMENT AND BEHAVIOR AFTER TRANSCATHETER VERSUS SURGICAL CLOSURE OF SECUNDUM TYPE ATRIAL SEPTAL DEFECT

Sarrechia I., De Wolf D., Miatton M., François K., Gewillig M., Meyns B., & Vingerhoets G. *Neurodevelopment and Behavior after Transcatheter versus Surgical Closure of Secundum Type Atrial Septal Defect.* J Pediatr, 2015. **166** (1):p. 31.38

ABSTRACT

Objective

To assess the neuropsychological and behavioral profiles of school-aged children treated for atrial septal defect, secundum type (ASD-II) with open-heart surgery or catheterization.

Study design

Patients (n = 48; mean age, 9 years, 3 months) and a matched healthy group (mean age, 9 years, 2 months) were evaluated with a shortened intelligence scale (Wechsler Intelligence Scale for Children, third edition, Dutch version) and a developmental neuropsychological test battery (Developmental Neuropsychological Assessment, second edition, Dutch version). Parents completed behavioral checklists (Achenbach Child Behavior Checklist for Children aged 6-18). Hospitalization variables were retrieved from medical files for studying associations with long-term neurodevelopment.

Results

Compared with the healthy matched controls, patients treated for ASD-II had significantly lower scores on subtasks underlying such Developmental Neuropsychological Assessment, second edition, Dutch version domains as Attention and Executive Functioning, Language, Working Memory, Sensorimotor Functioning, Social Cognition, and Visuospatial Information Processing. Only subtle differences, mainly in Visuospatial Information Processing, were found between the surgical repair and transcatheter repair groups. Socioeconomic status, longer hospital stay, and larger defect size were associated with neurocognitive outcome measures. Parents of patients reported more thought problems, posttraumatic stress problems, and lower school performance compared with parents of healthy peers.

Conclusion

After treatment for ASD-II, children display a range of neuropsychological difficulties that may increase their risk for learning problems and academic underachievement. Differences related to treatment were not found. Our results suggest that neurodevelopmental and behavioral follow-up at school-age is warranted in this group.

Keywords

Atrial septal defect secundum type • Behavior • Child Behavior Checklist • Congenital heart disease • Neurodevelopment

Introduction

Surgery and catheterization for symptomatic atrial septal defect, secundum type (ASD-II) have proven to offer excellent survival rates and functional outcome[1], yet little emphasis has been placed on the long-term neurodevelopment of this patient cohort. Few studies have addressed the impact of cardiac intervention to treat acyanotic congenital heart disease (CHD) on later neurocognitive function. Negative mental and behavioral sequelae after intervention for acyanotic heart defects have been documented[2-6]. Studies have reported a high prevalence of low-to-average intelligence scores, attentional dysfunction, and problems with visuospatial information processing and motor function in cohorts of acyanotic patients[2, 3, 5, 7-9]. Studies also have focused on understanding the various possible causes underlying neurobehavioral impairment, including genetics, surgical procedures, cerebral hypoperfusion, micro embolization, the inflammatory response, and the general psychological and physical strain caused by surgery and hospitalization[10-14]. More recently, the influence of family factors, such as socioeconomic status (SES) and parental stress, have received more attention. These noncardiac environmental factors can counterbalance the impact of risk factors and are protective against adverse developmental outcomes[4, 5, 13].

The aim of the present study was to evaluate neurocognitive and behavioral sequelae following different interventions for symptomatic ASD-II. We compared the neuropsychological profiles of children with corrected ASD-II and matched healthy controls. In addition, we evaluated the differential influence of treatment methods by comparing patients who underwent surgical closure and those who underwent transcatheter closure for ASD-II.

METHODS

Patients

The study cohort included patients treated for an ASD-II in 2 Belgian specialized heart centers, Ghent University Hospital and University Hospital Gasthuisberg Leuven. The selected patients underwent neurodevelopmental screening at school-age (6-12 years). Exclusion criteria were perinatal problems, preterm birth (<37 weeks gestational age), birth weight <2000g, other cardiac malformations, genetic abnormalities, and developmental syndromes. Out of 87 invited children, the parents of 48 children with ASD-II (55%) elected to participate in the study. For the surgical repair group, 62% of the respondents were enrolled; in the transcatheter repair group, 51%. Reasons for nonparticipation included diagnosis of a developmental syndrome (4.5%), family issues (3.5%), and no response (37%).

Surgical closure of ASD-II was performed via midline sternotomy with direct suture using mild to moderate hypothermic (range, 28-37°C) cardiopulmonary bypass. There were no significant differences in surgical defect repair between the 2 centers.

Percutaneous ASD-II closure was performed using a Figulla ASD occluder (Occlutech, Jena, Germany) at Ghent University Hospital, and transcatheter repair was achieved using an Amplatzer occlusion device (AGA Medical Corporation, Plymouth, Minnesota) at University Hospital Gasthuisberg Leuven. Both devices have proven to provide effective closure of ASD-II[15].

The patient cohort comprised 18 patients who underwent surgical repair and 30 patients who underwent transcatheter repair (mean age, 9 years, 3 months ± 1 year, 9 months). All 48 patients had undergone functional ASD-II repair and were considered healthy at the time of assessment. The healthy control group, consisting of 48 children, was recruited through approval of primary school boards and was matched with the patients on sex, age, and parental education. Parents completed demographic surveys. SES was determined using the Hollingshead Four-Factor Index[16], which combines parental occupational and educational level. Raw scores ranged from 24 to 66, with a higher score indicating higher social status. The 2 hospitals' Medical Ethics Committees approved the study, and written consent was

obtained from the parents of all patients. The study protocol was in accordance with the Declaration of Helsinki[17].

Neurodevelopmental assessment

The children's intelligence was assessed using a shortened version of the Wechsler Intelligence Scale for Children, third edition, Dutch version. In the Wechsler Intelligence Scale for Children, third edition, Dutch version, 2 verbal subtests (similarities and vocabulary) and 2 performance tasks (picture arrangement and block design) constitute a reliable measure of overall intelligence[18].

The Developmental Neuropsychological Assessment, second edition, Dutch version is a reliable test battery for assessing an extensive range of neurocognitive skills in children[19]. The Developmental Neuropsychological Assessment, second edition, Dutch version domains of Attention and Executive Functioning, Language, Memory and Learning, Sensorimotor Integration, Social Perception, and Visuospatial Processing were assessed. Outcome scores are expressed as age-adjusted standardized scores (mean ± SD, 10 ± 3), or percentile scores, which are considered process scores (<2nd to 75th percentile). These scores assess specific abilities or error rates that allow the clinician to evaluate a child's performance in more detail. Total test duration was 3 hours; breaks were provided during the test procedure when necessary to avoid fatigue.

The Achenbach Child Behavior Checklist for children aged 6-18 (CBCL-6/18)[20] was used to obtain standardized measures of various aspects of behavioral, social, and emotional functioning of the children as rated by their parents. The CBCL-6/18 contains problem behavior scales and competence scales, rated in terms of frequency on a 3-point Likert scale. The 113 items cluster into 8 syndrome scales. Three composite scales are computed—internalizing, externalizing, and combined—which constitute the total problem behavior. Specific classifications of behavioral questions represent clinical Diagnostic and Statistical Manual of Mental Disorders (DSM)-oriented scales. Outcome scores are expressed as t-scores.

Medical charts were retrieved for patient hospitalization data potentially associated with cognitive outcome measures (Table 1). Correlations with outcome measures and SES, age, and weight at intervention, total hospital stay, and defect

size were explored. Additional analyses were performed in the surgical repair group to study associations between outcome scores and time on extracorporeal circulation and level of hypothermia during the procedure.

Statistical Analyses

Normally distributed data are presented as mean ± SD; data that do not meet normality assumptions, as median (IQR). Demographic characteristics and cognitive outcome measures were compared between the patient group and matched controls. Nominal data were compared using the Fisher exact test. For data derived from the medical charts, median and IQR were calculated.

For evaluating Developmental Neuropsychological Assessment, second edition, Dutch version outcomes, ANOVA was used to analyze group contrasts. Percentile scores were analyzed by the nonparametric Mann-Whitney U test with the exact option for nonrelated samples. In comparisons of different treatment outcomes, SES was added as a covariate in the analyses. To control for multiple testing, P values were adjusted according to the Benjamini-Hochman false discovery rate[21]. Effect sizes were calculated to quantify the difference between groups. Corrections and effect sizes were applied to standardized scores and percentile scores separately. For parametric data, the Cohen d was computed, which determines effect size based on difference between 2 means divided by the pooled SD. For data that did not meet normality assumptions, the Mann-Whitney r was calculated. Effect size was classified as small (d= .20/r=.10), moderate (d= .50/r= .30), large (d= .80/r=.50) and very large (d = 1.3/r = .70). Effect sizes were calculated for equal samples (patients vs controls) and unequal sample sizes (surgical repair group vs transcatheter repair group), respectively.

Pearson and Spearman correlations (2-tailed) were used to explore associations between neuropsychological outcomes and medical variables for standardized and percentile scores, respectively.

RESULTS

Table 1 provides an overview of birth characteristics, demographic data, and hospitalization data, retrieved from medical charts. Birth weight and birth length differed significantly between patients and controls. No other differences were found, owing to the careful matching of the 2 groups.

Performance on intelligence assessment and neuropsychological screening is summarized in Table 2. Intelligence outcome scores showed no significant between-

group differences. Overall estimated intelligence and associated verbal and performance subtasks were within normal ranges and reflected small effect sizes (d 0.07-0.39).

In terms of the neuropsychological profile, between-group differences were evident in all domains assessed. Although standard scores were close to normal population means, moderate to large effect sizes ($d \geq 0.50$ / $r \geq 0.30$) were evident in the majority of the scores, where significant differences between groups were observed.

In the Attention and Executive Functioning domain, patients scored lower than controls on almost every outcome. On the subtest level, auditory attention, inhibition, design fluency, and sustained attention as measured by inhibition time yielded significantly lower results in the patient group. In the Language domain, performance on subtasks of comprehension of instructions and repetition of nonsense words was lower for patients compared with controls. Memory scores differed in terms of the recall of previously familiarized faces and the working memory aspect in word list interference. The patients scored significantly lower on the subtasks of the Sensorimotor Function domain, where imitation of hand positions, manual motor sequences, and visuomotor precision assessed refined motor skills. Theory of mind tasks in the Social Cognition domain elicited group differences. The significant value for the affect recognition subtask showed a trend after correction for multiple testing. Visuospatial competency was lower in the patient group for block construction and design copying.

Among the patient cohort, the surgical repair and transcatheter repair groups differed significantly in terms of SES, age at intervention, length of hospital stay, and defect size. SES was entered as a covariate in the analyses. Patients in the surgical repair group scored lower in the subtasks cued recall of a narrative and, more explicitly, visuospatial skills, assessment of motor and visual perceptual skills, and visuospatial analysis. However, following correction for multiple testing with the Benjamini-Hochmann method, none of these differences remained significant, and the 2 treatment groups showed no differences in long-term neurocognitive outcomes. Splitting the patient cohort reduced the power of our analysis; for example, according to power calculations, we would need 45 subjects in each group to reach 80% power to find a significant difference ($P < .05$) in full estimated IQ.

Of note is the pattern of the scores, with the surgical repair group scoring lower on the majority of the subtests, although the differences do not achieve statistical significance. The false discovery rate multiple testing correction discarded

some of the significant P values; however, in terms of clinical relevance, we can discern particular moderate to large effect sizes ($d \geq 0.50$ / $r \geq 0.30$) in the Intelligence, Inhibition Memory and Learning, and Visuospatial Information Processing domains, suggesting meaningful differences between treatment groups.

Table 3 presents CBCL-6/18 data for patients vs controls and for the surgical repair group vs the transcatheter repair group. Compared with healthy peers, parents of patients reported more thought problems and posttraumatic stress disorder (PTSD) symptoms in the DSM-oriented scales. The parents of patients also rated their child's school performance significantly lower than the parents of controls, leading to a higher percentage of patients repeating a grade. No significant differences were found between the surgical repair and transcatheter repair groups. Both comparisons generated relatively small effect sizes.

SES was positively associated with a number of outcomes, including full-scale estimated IQ ($r = 0.536$; $n = 48$; $p < 0.001$), inhibition time ($r = 0.377$; $n = 48$; $p < 0.01$), comprehension of instructions ($r = 0.353$; $n = 48$; $p < 0.05$), repetition of nonsense words ($r = 0.417$; $n = 46$; $p < 0.01$), manual motor sequences ($r = 0.303$; $n = 48$; $p < 0.05$), theory of mind–verbal ($r = 0.349$; $n = 48$; $p < 0.05$), and block construction ($r = 0.378$; $n = 48$; $p < 0.01$). This demographic factor also was associated with significant differences on the CBCL-6/18 for PTSD symptoms ($r = −0.279$; $n = 48$; $p < 0.05$), need for special education ($r = 0.285$; $n = 48$; $p < 0.05$), and repeating a grade ($r = 0.426$; $n = 48$; $p < 0.01$).

Correlational analysis identified only 2 medical factors as associated with suboptimal outcome measures in patients compared with controls. Longer length of hospital stay and larger defect size were correlated with lower performance in at least 4 neuropsychological scores. The former was significantly associated with memory for faces delayed ($r = −0.328$; $n = 42$; $p < 0.05$), manual motor sequences ($r = −0.286$; $n = 48$; $p < 0.05$), block construction ($r = −0.303$; $n = 48$; $p < 0.05$), and the total score of design Copying ($rs = −0.335$; $n = 47$; $p < 0.05$), and its subtasks motor score ($r = −0.400$; $n = 47$; $p < 0.01$) and local score ($r = −0.331$; $n = 47$; $p < 0.05$). Defect size was negatively correlated with memory for faces delayed ($r = −0.331$; $n = 42$; $p < 0.05$), the contextual part of the theory of mind task ($r = −0.381$; $n = 48$; $p < 0.01$), design copying total score ($rs = −0.498$; $n = 47$; $p < 0.001$), and its motor score ($r = −0.431$; $n = 47$; $p < 0.01$). In the surgical repair group, duration of extracorporeal circulation and level of hypothermia did not demonstrate any relevant associations with neurocognition at follow-up.

Table 1. *Demographics*

	ASD-II	*Controls*	*p*	*ASD-II-surg*	*ASD-II-cath*	*p*
N	48	48		18	30	
Sex	♂:19 ♀:29	♂:19 ♀:29	*1.0* χ^2	♂:6 ♀:12	♂:13 ♀:17	.493 χ^2
Test age	9y3m±1y9m	9y2m±1y9m	*.845*	9y2m±2y2m	9y3m±1y7m	*.952*
Birth weight (gr)	3228±491	3497±570	*.015**	3316±387	3175±543	*.341*
Birth length (cm)	49.5±2	50.8±2.6	*.008***	49.8±2	49.3±2	*.478*
Apgar (5 min)	<4: 0% 4-6: 0% 7-10:100%	<4:0% 4-6:0% 7-10:100%	*ns*	<4: 0% 4-6: 0% 7-10:100%	<4:0 % 4-6: 0% 7-10: 100%	*ns*
SES	40.1 ± 8	43.2 ± 7.1	*.055*	37.2 ± 6.6	41.9 ± 8.4	*.045**
Age at intervention (min-max)	-	-		2y9m±1y8m 4.8m – 6y7m	4y2m±1y7m 6.4m – 7y6m	*.014**
Weight at intervention (pc)	-	-		3-10: 72.2% 25-50: 16.7% 75-90: 11.1%	3-10: 31% 25-50: 31% 75-90: 38%	*.054*^{E}
Hospital stay (days)	-	-		7 (6-7)	2 (2-2)	*<.001***
Defect size (mm)	-	-		19 (14-21)	11 (10-13)	*<.001***
ECC time (min)	-	-		38.5 (32-49)	-	
Level of hypothermia (C°)	-	-		32 (31.5-36.2)	-	

Medical data are presented as median (interquartile range), except for age (mean ± SD)
Nominal data: χ^2 with Exact test (E)

Table 2. *Neuropsychological performance*

	ASD-II patients	*ASD-II controls*	*Adj. p*	*Effect size d/r*	*ASD-II surgery*	*ASD-II catheter*	*Adj. p*	*Effect size d/r*
WISC-III-NL								
Estimated full scale IQ	102.9±15.7	107.9±10.6	.176	.37	97.4±14.8	106.3±15.6	.516	.58
Similarities	12.±3.1	12.4±2.3	.738	.07	11.8±3.4	12.5±2.9	.860	.22
Picture arrangement	9.5±3.4	10.7±2.6	.176	.39	8.3±3.4	10.3±3.2	.516	.61
Block Design	9.9±2.8	10.8±2.9	.176	.31	8.9±2.7	10.6±2.8	.516	.61
Vocabulary	10.2±2.6	11±2.2	.176	.33	9.4±2.0	10.7±2.9	.596	.49
NEPSY								
Auditory Attention and Executive Functioning								
Auditory Attention(pc)	50(25-75)	75(75-75)	<.001**	.38	62(25-75)	50(25-75)	1.0	0
-Commission errors (pc)	75(10-75)	75(75-75)	.029*	.25	50(10-75)	75(10-75)	.496	.19
-Omission errors (pc)	37.4(25-75)	75(50-75)	.029*	.24	75(25-75)	25(25-75)	.571	.14
Response Test(pc)	50(25-50)	50(50-68.7)	.029*	.29	25(25-50)	50(21-50)	.571	.14
Commission errors	25(10-25)	75(56.2-75)	<.001**	.64	17(10-31)	25(10-25)	.660	.11
-Omission errors	25(25-68.7)	75(50-75)	.009**	.35	(25-50)	50(25-75)	.556	.17
-Inhibition errors	25(10-75)	25(25-75)	.251	.15	25(21-75)	25(10-75)	.821	.05
Design Fluency	9.2±1.8	10.5±2.4	.010**	.61	8.7±1.7	9.5±1.9	.617	.43
Inhibition (pc)	50(50-50)	50(50-75)	.029*	.25	50(50-62)	50(50-50)	1.0	0
-time	10±2.4	11.1±1.9	.033*	.50	9.4±2.0	10.5±2.5	.617	.47
Language Domain								
Comprehension of Instructions	10.6±2.9	11.9±2.4	.024*	.48	9.8±2.7	11.1±2.9	.617	.46
Repetition of Nonsense Words	9.9±2.6	12.1±1.8	<.001**	.98	9.2±2.3	10.4±2.7	.617	.46
Speeded Naming								
Total (pc)	50(25-50)	50(25-50)	.251	.13	25(25-50)	50(25-50)	.464	.20
Time (pc)	75(75-75)	75(75-75)	.251	.11	75(75-75)	75(75-75)	.688	.09
Word Generation								
Semantic	9.8±2.7	10.2±2.4	.534	.15	9±2.1	10.3±2.9	.617	.49
Linguistic (pc)	50(10-75)	50(25-50)	.938	0	25(7-62)	62.5(21-75)	.440	.23
Memory and Learning Domain								
Memory for Faces	9.8±3.2	9.8±2.7	.977	0	9.6±3.3	9.9±3.2	.997	.09
Delayed	10.3±2.9	11.8±2.7	.029*	.53	9.2±3.4	10.8±2.6	.617	.54
Memory for Names	9.6±2.9	9.3±2	.571	.12	8.6±2.4	10.2±3	.617	.57
Narrative Memory	10.1±2.3	10.8±1.7	.140	.34	10.4±2.3	10±2.3	.617	.17
Cued recall (pc)	50(25-75)	50(50-75)	.513	.07	50(25-50)	62.5(50-75)	.123	.32
Word List Inference								
Working memory	10.4±2	11.5±1.9	.019*	.56	10.4±2	10.4±2	.997	0
Word recall	11.6±2.6	11.1±2.4	.478	.19	11.1±2.5	11.9±2.7	.617	.30

Table 2. *Neuropsychological performance*

	ASD-II patients	*ASD-II controls*	*Adj. p*	*Effect size d/r*	*ASD-II surgery*	*ASD-II catheter*	*Adj. p*	*Effect size d/r*
Sensorimotor Domain								
Imitating Hand Positions	8.9±2.4	10.5±1.6	<.001**	.78	8.8±2.4	9.1±2.4	.997	.12
Manual Motor Sequences	11.6±3	13.4±1.9	.003**	.71	10.7±3.8	12.2±2.4	.617	.50
Visuomotor Precision								
-Time (pc)	50(25-50)	50(50-75)	<.001**	.36	50(25-56)	25(25-50)	.556	.15
-Error (pc)	25(10-68)	25(10-50)	.746	.03	50(19-75)	25(10-56)	.688	.08
Social Perception Domain								
Affect Recognition(pc)	25(5-50)	50(25-50)	.057	.22	17.5(4-56)	25(8.7-50)	.688	.08
Theory of Mind								
-Verbal Task	10.6±2.8	12±2.2	.015*	.55	10±2.6	10.9±3	.823	.31
-Contextual Task	9.8±2.6	11.3±1.9	.003**	.65	9.1±2.4	10.2±2.6	.617	.43
Visuospatial Processing Domain								
Block Construction	10.4±2.4	12.3±2.2	<.001**	.82	9.3±1.9	11.1±2.5	.414	.78
Design Copying (pc)	10(5-25)	10(10-25)	.029*	.25	5(2-13.7)	10(7.5-25)	.101	.35
-Motor	9.7±3.1	11.9±2.4	<.001*	.79	7.9±3.2	10.8±2.5	.072	1.04
-Global (pc)	25(25-50)	25(25-50)	.343	.11	25(10-31)	25(10-50)	.402	.23
-Local	8.5±2.2	9.5±2	.033*	.47	7.5±2.4	9.1±1.9	.252	.76
Geom. Puzzles (pc)	50(25- 50)	50(25-75)	.408	.09	25(21-50)	50(43.7-75)	.101	.37
Route Finding (pc)	25(10-43.7)	25(25-50)	.251	.14	25(10-25)	25(25-50)	.101	.34

Between-group differences were explored using AN(C)OVA for standardized scores (mean ± SD) and the Mann-Whitney U test for process scores, expressed as percentile (median and UQR).
d: Cohen d effect size, r:Mann-Whitney effect size
p-value adjusted to the Benjamini-Hochberg false discovery rate
*p<.05
**p<.01

Table 3. *Behavioral functioning as measured by parental CBCL-6/18 responses*

CBCL	ASD-II	Controls	*Adj. p*	Effect size d / r	ASD-II surgery	ASD-II catheter	*Adj. p*	Effect size d / r
Problem behavior Scales	Mean±SD	Mean±SD			Mean±SD	Mean±SD		
Withdrawn / depressed	54.4±5.7	53.6±5.4	.525	.06	53.9±6.4	54.7±5.4	.469	.10
Somatic complaints	55.3±5.7	53.9±5.1	.234	.12	53.7±6	56.3±5.3	.053	.28
Anxious/ depressed	54.3±5.3	53.8±5.4	.505	.06	54±5.9	54.4±5	.384	.12
Social problems	54±4.8	52.3±3	.068	.18	54.1±5	54±4.7	.962	0
Thought problems	56.3±7.4	52.6±3.8	.020*	.23	53.6±6.4	58±7.5	.083	.25
Attention problems	55.6±7.6	52.4±2.6	.078	.18	56.5±9.2	55±6.6	.526	.09
Rule breaking behavior	52.7±3.7	52±3.7	.519	.06	52±2.9	53.1±4.1	.311	.14
Aggressive behavior	53.6±5.1	52.1±3.9	.125	.15	53.1±5.9	53.8±4.6	.497	.10
Internalizing	51.5±9	49.5±8.7	.291	.22	49.5±9.8	52.6±8.4	.191	.33
Externalizing	47.5±10.1	45.9±8.4	.413	.17	46.1±10.3	48.3±10.1	.272	.21
Total problem score	50±10.1	46.6±7.7	.067	.37	48.8±10	50.7±10.3	.222	.18
DSM-Clinical scales								
Affective problems	55.2±5.8	53.8±5.1	.209	.12	54±5	56±6.2	.251	.16
Anxiety problems	55.8±6.4	53.7±5	.087	.17	53.8±5.4	57±6.7	.130	.22
Somatic problems	55.2±6.3	54.4±5.8	.466	.07	53.8±7.3	56.1±5.6	.074	.25
Attention/Hyperactivity problems	54.5±6.1	52.4±3.7	.137	.15	54.5±6.1	54.4±6.1	.918	.01
Oppositional Defiant problems	53.5±4.9	52.1±3.2	.445	.07	52.9±4.5	53.9±5.2	.567	.08
Conduct problems	52.7±4.5	52±4	.694	.04	52.4±5	52.9±4.3	.378	.12
Sluggish cognitive tempo	54.8±4.5	52.5±3.2	.224	.12	54.8±7.1	54.8±6.3	.838	.03
Obsessive/Compulsive problems	55.8±7.6	53.5±5.1	.366	.09	56.1±8.2	55.6±7.4	.858	.02
Post-Traumatic Stress problems	56.4±6.5	53±4.6	.019*	.23	55.5±7	56.9±6.2	.385	.12
Competence scales								
Activity	40.8±8.8	38.9±8.6	.280	.11	37.9±7.2	42.6±9.2	.114	.22
Social	50±7.9	49.9±6.7	.681	.04	48.7±6.6	50.8±8.7	.220	.17
School	46.8±9.2	50.8±5.3	.057	.19	45.2±10.7	47.7±8.4	.473	.10
Special education	Yes: 4.2% No: 95.8 %	Yes: 0% No: 100%	.495E		Yes:5.6% No:94.4 %	Yes: 3.3% No: 96.7%	1.0^{E}	
Repeating school year	Yes: 16.7 % No: 83.3%	Yes: 0% No: 100%	.006$^{**\,E}$		Yes: 22.2% No:77.8%	Yes: 13.3% No: 86.7%	.692^{E}	
School problems	Yes: 31.3% No: 68.8%	Yes: 8.3% No:91.7%	.005$^{**\chi^2}$		Yes: 33.3% No: 66.7%	Yes :30% No: 70%	.809$^{\chi^2}$	
Total competence	44.8±9.4	44.2±9.3	.747	.06	42.5±8.4	46.1±9.8	.452	.39

Subscales: Mann-Whitney U test (with exact option); composite scales: AN(C)OVA.
χ2- test (Fisher's exact test^{E})
*p<.05
**p<.01

DISCUSSION

Given the diverse nature of the neurocognitive impairments in children with ASD-II, affected children are at risk for learning problems and subsequent academic underachievement. Although patients with more complex cyanotic cardiac pathologies often deal with unstable hemodynamics and metabolic acidosis and require advanced surgical repair, studies frequently report similar adverse neurodevelopmental outcomes in acyanotic cohorts[4, 22]. Attentional shortcomings, working memory problems, language deficits, adverse socialization behavior, and especially impaired motor functioning and weak visuospatial skills have been identified in the exploration of cognitive sequelae after (acyanotic) CHD repair[2, 3, 7, 9, 23]. Larger defect size and longer hospital stay were associated with poor neuropsychological outcome measures, particularly in the visuomotor and visuospatial domain. The former may reflect the progressive nature of the left-to-right shunt on the central nervous system, extending until cardiac repair. The latter factor has been associated with lower functional and developmental outcomes in other CHD cohorts[8, 24]. It should be noted that normal hospital stay for children treated surgically for an ASD-II is 4-5 days. It is possible that the children in our cohort had to cope with more postoperative problems, prolonging their hospital stay.

Even though transcatheter closure of ASD-II is favored over surgical closure because of the shorter hospital stay and lower post procedural complication rates[25], we found almost no differences in neuropsychological outcomes related to treatment method.

Studies exploring the possible detrimental effects of surgical closure of ASD-II on neurodevelopment have yet to provide complete answers. Visconti et al.[3] showed that, after adjusting for parental IQ, surgical closure of ASD-II was associated with a 9.5-point deficit in full-scale IQ and visuospatial problems, whereas a group that underwent transcatheter repair had more attentional problems and impulsivity. Our surgical repair group's performance on visuospatial information processing tasks is comparable with those findings, although we found no significant difference in attention scores between our 2 treatment groups. Stavinoha et al.[26] evaluated the neuropsychological outcomes of 18 children undergoing surgical repair of ASD. They compared preoperative and postoperative cognitive outcomes, but failed to demonstrate a clear effect of the duration of

cardiopulmonary bypass on neuropsychological status within 6 months after corrective surgical repair. Outcome scores were within normal ranges but clearly below expected norms for all cognitive functions evaluated.

Quatermain et al.[27] prospectively assessed neuropsychological domains in children with acyanotic CHD before and after surgical repair. Outcome scores were within normal ranges, although individual variability in scores was common. The authors concluded that a mild cognitive decline seen after intervention for acyanotic CHD is not necessarily attributable to the use of cardiopulmonary bypass. The population in this study underwent corrective repair at older ages and thus possibly had less urgent conditions compared with our cohort. It is possible that the subtle cognitive effects of corrective repair at a young age may become apparent many years after medical interventions for acyanotic CHD.

The correlations between SES and numerous cognitive outcomes in our patient cohort is in line with those reported in previous studies[4, 5, 13], indicating that the environment in which these children are raised can serve as a protective factor against adverse neuropsychological development.

Compared with parents of healthy controls, parents of patients reported more thought problems and higher scores on the PTSD DSM scale. The thought problems scale encompasses such items as compulsions and obsessions, as well as fears and psychotic behavior. The DSM-derived PTSD scale reflects symptomatology that adheres to the clinical classification of PTSD in individuals with acyanotic CHD. These findings apparently agree with those of previous studies in children with CHD[3-5], confirming the prevalence of internalizing behavior problems. Internalizing behavior problems can lead to increased risk for depression, anxiety, and social withdrawal. Behavioral problems can put additional strain in the lives of children treated for ASD-II that may persist and affect peer relationships and ultimately the quality of adult life[28].

Hospitalization can be a great stressor for both children[12] and their parents[29]. Parental style and family dynamics are non-negligible factors in long-term cognitive and social development. High levels of stress in the parent–child relationship have been found to affect cognitive skills and socialization behavior in children[5], in line with our present findings. Whether these results reflect actual PTSD problems in the child rather than parent-induced stress and anxiety after diagnosis, intervention,

and hospitalization is unclear. In our patient cohort, lower SES was correlated with high rates of the need for special education, repeating a grade, and PTSD symptoms. These families' coping strategies may be less well developed, also affecting the child's neurobehavioral development. Consequently, parents may be less inclined to notice cognitive or behavioral difficulties in their children and to seek professional help. Schreier et al.[29] described the interaction of family dynamics after pediatric hospitalization, with parents displaying PTSD symptoms correlating with child-reported symptoms. Family expressiveness was identified as an efficient coping strategy.

A large body of literature addresses the neuropsychological outcomes of children with CHD at a very young age, when myelination of neurologic structures is incomplete and higher neurocognitive functions have yet to mature. The subtle effects of hospitalization-, anesthesia, and procedure-related factors may become apparent only many years after surgery and are difficult to detect and quantify during early childhood. In addition, the idea that induction of anesthesia at a young age to improve the tolerance of surgical procedures is detrimental to neurodevelopment is under consideration. Information on the neurotoxicity of analgesic agents and their influence on the young brain is accumulating. Neurologic structures mature at different rates, and it can be assumed that the vulnerable period of the young brain extends well past the first 2 years of life[30]. This may eventually affect the plasticity of the developing brain and contribute to adverse long-term cognitive outcomes in children with CHD.

The growing into deficit hypothesis[31] can serve to clarify the chain of events. Children at risk for central nervous system injury due to a medical condition can function adequately at young school-age but are hindered when academic demands begin to tap cognitive functions that were neurologically susceptible to injury and thus suboptimal from the start. This also implies that assessment of neurocognitive functions in very young children may have limited predictive value for later cognitive performance and academic achievement. The effects of the heart lesion, hospitalization, and interventional procedures on the developing brain all likely contribute to the course of events producing adverse neurodevelopmental outcomes at school-age.

Limitations of the present study include possible selection bias and the lack of preoperative screening. We cannot ascertain whether the children in the patients group had neurocognitive difficulties before treatment, recognizing that the reliability and validity of assessment increase with age. Before age 6 years, it is particularly difficult to accurately evaluate a child's cognitive abilities. In addition, obtaining a uniform perspective on the neuropsychological profiles of children with CHD has proven difficult. Numerous studies focus on different diagnoses and specific interventions, study divergent age ranges, and use various screening instruments that may measure different aspects of neurocognitive domains. This limits the comparability and generalizability of results and is the main factor in the conflicting findings obtained from this type of research. Marino et al.[32] published formal guidelines for screening children with CHD at risk for developmental disorders, taking protective factors, such as family and environment, into account. In this way, consistency in developmental follow-up across time can be improved. Moreover, it remains a challenge to find a suitable control group for children with CHD that is comparable in the most important aspects related to this condition, from the psychological and physical distress of hospitalization and surgery to central nervous system risk factors that put these children at risk for hypoperfusion of vital organs, including the developing brain. Our use of 2 clinical groups in this study partially addresses this issue, given that these children were diagnosed with the same cardiac pathology but underwent different treatments depending on defect size and -location. Despite the small sample size and restricted generalizability owing to the study's retrospective nature, our results are in line with previous findings in this clinical group.

CONCLUSION

It is important to enhance knowledge and awareness among clinicians concerning long-term neurocognitive consequences following a diagnosis of CHD, and also to consider parental reports of the child's neurobehavioral functioning in school during the follow-up visits after intervention. Appropriate referral to a neuropsychologist and guidance for parents then can be realized when applicable. Future research should address the differential influence of patient-specific and medical factors that put these children at risk and include pretreatment neurologic examinations.

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CHAPTER 6

NEUROCOGNITIVE DEVELOPMENT AND BEHAVIOR IN SCHOOL-AGED CHILDREN AFTER SURERY FOR UNIVENTRICULAR OR BIVENTRICULAR CONGENITAL HEART DISEASE

Sarrechia I., Miatton M., De Wolf D., François K., Gewillig M., Meyns B., & Vingerhoets G. *Neurocognitive development and behavior in school-aged children after surgery for univentricular or biventricular congenital heart disease*. Eur J Cardiothorac Surg 2015; doi:10.1093/ejcts/ezv029

ABSTRACT

Objective
To assess the long-term neuropsychological and behavioral profile of school-aged children who were treated for univentricular heart (UVH) conditions or biventricular heart defect (BiVH) in infancy in a cross-sectional study design.

Methods
Sixty-three patients, 17 UVH (13 males, 4 females) and 46 BiVH (19 males, 27 females), were assessed at a mean age of 9.1 years (2.2 years) with an intelligence and neuropsychological test battery. Results were compared between subgroups (UVH, BiVH and a healthy control group). Associations between cognitive outcome, medical and socio-demographic factors were explored. Parents completed the Child Behavior Checklist (CBCL).

Results
Mean intelligence and neuropsychological scores were found within normal ranges for all diagnostic groups. Significant differences between UVH patients and controls emerged on auditory sustained and alternating attention, fine motor skills, visuospatial information processing, and to a lesser extent, memory performance. Parents of UVH patients reported more externalizing problems and school problems. Patient groups did not differ on neuropsychological outcome measures, nor on behavioral problems as rated by parents.

Conclusion
After Fontan completion, patients at school-age display intelligence scores within normal population-based ranges. However, they were found at risk for subtle shortcomings in attention, fine motor skills, visuospatial information processing and externalizing behavior problems. Considerations pertaining to neurobehavioral outcome at school-age are discussed.

Keywords
Congenital heart defect • Hypoplastic left heart • Tricuspid atresia • Neuropsychology • Neurodevelopmental outcome

INTRODUCTION

Advanced surgical staged palliation is the current treatment for children with a univentricular heart (UVH), a once considered fatal condition. The prevalence of this complex congenital heart disease (CHD) is estimated at 0.08–0.09 per 1000 births and represents ~2% of all CHD's[1]. These children often present at birth with congestive heart failure, cyanosis, poor feeding and respiratory distress, making immediate intervention imperative.

With the growing number of survivors following treatment for complex CHD, neurodevelopmental outcome has been highlighted throughout the last decades. Of all cohorts with CHD, those with UVH suffer from the poorest cognitive outcome. At preschool-age, these children exhibit mental and psychomotor developmental indexes in the low-to-average range as assessed by the Bayley Scales of Infant Development (BSID)[2-5]. At school-age, when broader cognitive functions develop, low-to-average intelligence scores have been described in children treated for UVH in early and recent reports[6, 7]. Studies have documented subtle problems in attention and executive functioning, language, but predominantly in motor functioning and visuospatial information processing[4, 8-10]. Altogether, it puts subgroups of children with UVH at risk for academic underachievement and unemployment as they progress into adulthood[11].

Researchers have attempted to discover etiological factors underlying adverse cognitive functioning, but with varying success rates. Pre- and postoperative brain injuries, as well as genetic anomalies are common in this clinical population[5, 7, 12]. Intraoperative management and postoperative events possibly adversely affecting developmental outcomes have all been the focus of previous research efforts[5, 12]. Recently, evidence has been found for non-modifiable factors such as socio-economic status, genetics, neurological anomalies and parenting style to explain the adverse development of these children[5, 13].

The present study was set up to delineate and update the cognitive profile of children diagnosed with and treated for hypoplastic left heart (HLH) or tricuspid atresia (TA), considered as the UVH cohort. We compared cognitive outcomes with those of a matched healthy control group (UVH controls) and with those with surgical repair of a biventricular heart defect (BiVH), for an atrial septum defect secundum type (ASD-II) or ventricular septum defect (VSD) in infancy. We

hypothesized that children treated for UVH would display more adverse neuropsychological functioning, due to preoperative hypoxia, prolonged cyanotic state, hemodynamic instability, multiple surgical procedures and subsequent long hospitalizations in infancy and early childhood.

METHODS

Patients

Patients treated surgically for UVH (HLH/TA) and BiVH (ASD-II/VSD) were selected in two specialized heart centers, Ghent University Hospital and University Hospital Gasthuisberg Leuven (Flanders, Belgium). They were assessed with an intelligence screening and an extensive neuropsychological test battery at school-age (6–12 years).

Exclusion criteria for the UVH cohort were severe genetic abnormalities interfering with normal mental development (Down syndrome, Noonan syndrome, velocardiofacial syndrome, Di George syndrome), other developmental syndromes and cerebral palsy. BiVH patients were excluded if there was evidence for perinatal problems, preterm gestational age (<37 weeks), birth weight <2000 g, other cardiac malformations, genetic abnormalities or developmental syndromes. Out of 107 invited, 63 parents of CHD patients (59%) responded positively to our appeal and participated. In Ghent University Hospital almost all parents of every eligible UVH patient agreed to participate in the study (12/14). In Leuven University Hospital, other studies competing for participation in the same clinical sample of UVH patients resulted in participation of 5 from 8 invited. Non-responders did not provide any demographic data, nor gave permission to review their medical files.

Included patients completed all steps of the assessment procedure. The clinical population consisted of 17 patients who had UVH treatment (HLH: 8/TA: 9) and 46 BiVH patients (VSD: 28/ASD-II: 18). Surgical palliation or defect repair was performed in both groups according to diagnosis- and institution-specific protocols.

The UVH group underwent staged surgical palliation during 2000–2009, initialized with the Norwood operation or pulmonary artery banding and concluded with the Fontan/total cavopulmonary connection operation. In the HLH cohort, 6 of 8 patients had ante grade flow in their aortic arch prior to the Norwood procedure. Patients with BiVH were treated during 1999–2010 with one single open-heart surgery with mild-to-moderate hypothermic (25–37°C) cardiopulmonary bypass.

The healthy control group was recruited through approval of primary school boards and was matched with each patient in terms of gender, age and parental education level. Parents completed demographic surveys.

The Hollingshead Four-Factor Index[14] was calculated for socio-economic status (SES) by combining parental occupational and educational level. Raw scores ranged from 24 to 66, a higher score indicating higher social status. Both the medical ethics committee of Ghent University Hospital and Gasthuisberg Leuven approved the study and parental written consent for the study and publication of the results was obtained.

Neurodevelopmental testing

Intelligence was assessed with a short version of the WISC-III-NL (3rd edn, Dutch version). Two verbal subtests (Similarities and Vocabulary) and two performance tasks (picture arrangement and block design) constituted a reliable measure of overall intelligence[15].

The NePsy (a Developmental Neuropsychological Assessment, 2nd edn, Dutch version)[16] is a customizable test battery to assess an extensive range of neurocognitive skills in school-aged children.

In a scientific statement of the American Heart Association, the NePsy was listed as a valid and reliable instrument to assess a variety of neuropsychological functions in children treated for CHD[17]. Domains of Attention and Executive Functioning, Language, Memory and Learning, Sensorimotor Integration, Social Perception and Visuospatial Processing were assessed.

Outcome scores are expressed as age-adjusted standardized scores (mean: 10, SD: 3), or percentile scores, which are considered to be process scores (pc < 2–pc75). These scores assess specific abilities or error rates that enable the clinician to evaluate a child's performance in more detail.

Behavioral assessment

The Achenbach Child Behavior Checklist for Children aged 6–18 (CBCL-6/18)[18] was used to obtain standardized measures of behavioral, social and emotional functioning of the children, rated by their parents. This questionnaire contains problem behavior scales and competence scales, to be rated in frequency on a three-point scale. Three composite scales are computed: internalizing scale,

externalizing scale and grouped together, these scales constitute the total problem behavior.

Statistical analysis

Data were analyzed using the SPSS version 21.0 statistical Package (SPSS, Inc., Chicago, IL, USA). Normality was checked by Kolmogorov–Smirnov tests. Normally distributed data are presented as means with standard deviation; median and interquartile ranges are given for data that did not meet normality assumptions. Demographic characteristics and cognitive outcome measures are compared between patient groups and the matched controls. Nominal data were compared using Fisher's exact test. For data derived from the medical charts, median and interquartile ranges were calculated.

For matched samples (UVH vs controls), paired t-tests and Wilcoxon signed-rank tests were applied to study group differences. Analysis of variances (ANOVAs) and Mann–Whitney U-tests were used to examine differences between patients (UVH vs BiVH). In the latter analyses, ANOVAs were adjusted for gender. To control for multiple testing, p-values were adjusted according to the Benjamini-Hochman false discovery rate[19].

In addition, effect sizes were calculated to examine clinically meaningful differences next to statistical significance. For parametric data, Cohen's d was computed to indicate the standardized difference between two means. For data that did not meet normality assumptions, Mann–Whitney's or Wilcoxon's r was calculated. Effect sizes are defined as small, d = 0.20/r = 0.10; moderate, d = 0.50/r = 0.30; large, d = 0.80/r = 0.50 and very large, d = 1.3/r = 0.70. Corrections and effect sizes were applied to standardized norm scores and percentile scores separately.

RESULTS

Patient population

Patients with HLH and TA did not differ significantly on demographic characteristics, neuropsychological or behavioral outcome; they were therefore considered as one group (UVH) in further analyses.

The comparison of the total group of UVH patients and controls did not elicit significant differences in demographics due to matching efforts (Table 1). When comparing the UVH group and the BiVH group, there was a significant difference in gender distribution. We controlled for this variable in further analyses by adding it as an extra between-subjects factor. The mean SES was middle class.

When compared with BiVH patients, the UVH patient group was significantly younger and weighed less at the time of first intervention. Cumulative lifetime durations of hospitalization, intensive care unit (ICU) stay, surgery, extracorporeal circulation, clamp time, duration of anesthesia and postoperative intubation time elicited significant group differences (Table 2). We identified one child (with TA) with postoperative convulsions. Additional brain imaging data showed bilateral posterior lesions. The patient was treated successfully with anticonvulsant medication. No other neurological problems were noted in the UVH cohort.

Neurocognitive assessment

Univentricular heart vs controls.

Mean estimated intelligence in the UVH group was 101 (range: 73–130); most intelligence scores were within normal ranges and did not differ from controls (Table 3).

Considering the neuropsychological assessment, significant differences were found in the Attention and Executive functioning domain, in Auditory Sustained and Shifting Attention, and Design Fluency. These results elicited medium to large effect sizes (d/r = 0.42–0.67).

A significant difference emerged between UVH patients and controls in the cued recall of a narrative in the Memory domain, with a medium effect size (r = 0.39). Significant differences were found in the domain of Sensorimotor functioning in fingertip tapping and manual motor sequences scores verged on significance (P = 0.051). These scores evoked medium to large effect sizes (d = 0.47–0.83). Patient Visuospatial information processing skills were found different from controls in

Design Copying, Total, Motor and Local score, resulting in medium to very large effect sizes (d/r = 0.39–1.2). Performance on block construction elicited a clear trend towards significance (P = 0.058).

Besides these significant group differences, it should be noted that the majority of mean and median scores were within normal ranges of population-based norms. Multiple testing correction discarded some of these statistically significant findings. We opted to interpret the clinical meaningful group differences.

Univentricular heart vs biventricular heart defect.

UVH patients obtained significantly lower scores when memorizing and recalling faces, but these scores reflected a small effect size (d = 0.13). Biventricular heart patients scored lower than the UVH group on a task of route finding, demonstrated by a small to medium effect size (r = 0.26) (Table 3).

Multiple testing correction discarded the statistically significant finding on memorizing and recalling faces. We interpreted the meaningful findings.

Behavioral functioning

Completing the CBCL, parents of UVH patients reported significantly more externalizing and total behavior problems when compared with ratings of the matched control group (Table 4).

A trend towards more internalizing behavior problems was demonstrated (P = 0.056). These results were accompanied by medium to large effect sizes (r = 0.32–0.42). School functioning was found worse for the UVH group when compared with controls.

Forty-seven percent of the parents of the UVH group reported school problems, which translated into repeating a grade and receiving special education in ~12% of the cases.

No significant differences appeared when comparing the UVH and BiVH patients; small to medium effect sizes were demonstrated (d = 0–0.33).

Associations with clinical and demographic variables for univentricular heart treatment

Spearman's rho analysis revealed a negative association between cumulative lifetime ICU stay and performance of auditory sustained attention (r_s = −0.587, N = 17, p = 0.013) and the aforementioned trend towards significance of the scores on block construction (rs = −0.589, N = 17, p = 0.013). A negative relationship was found between cumulative intubation time and the ability to shift attention and

inhibit pre-planned and on-going response mechanisms (r_s = −0.556, N = 13, p = 0.048). The total duration of mechanical ventilation during lifetime also showed an inverse association with fingertip tapping scores (r_s = −0.509, N = 17, p = 0.037).

Of the innate patient characteristics, pregnancy duration seemed to explain some of the variance in outcome scores of design copying; the motor score (r_s = −0.607, N = 17, p = 0.01).

Fingertip tapping scores were significantly related to birth weight (r_s= 0.737, N = 17, p = 0.001). Memory performance on a task of recalling a narrative with given cues was positively associated with SES (r_s = 0.515, N = 16, p = 0.041).

Cumulative lifetime duration of hospital stay, duration of surgery, prolonged time on ECC or aortic cross-clamp, nor duration of anesthesia elicited significant relations with adverse cognitive outcome scores. In addition, no correlations were found between patient characteristics or medical data and the composite scales of the CBCL.

Table 1. *Demographics*

	UVH patients	UVH Controls	p^a	BiVH patients	p^b
N	17	17		46	
Sex	♂:13 ♀:4	♂:13 ♀:4	*1.0* χ^2	♂:19 ♀:27	*.013** χ^2
Mean Test age, y:m (SD)	9.1 (2.1)	9.2 (2.1)	*.220*	9.0 (2.2)	*.964*
Mean Birth weight, gr (SD)	3269 (446)	3593 (564)	*.133*	3250 (476)	*.884*
Mean Birth length, cm (SD)	49.2 (3.1)	51.4 (2.6)	*.110*	49.5 (2.1)	*.583*
Mean Pregnancy duration , days (SD)	276 (12)	279 (10)	*.486*	273 (11)	*.484*
Apgar score 1 min	<4: 7.1% 4-6: 14.3% 7-10: 78.6% <4: 0%	<4:0 % 4-6:11.1% 7-10: 88.9% <4: 0%	*1.0*^{E}	<4: 0% 4-6: 5.4% 7-10: 94.6% <4: 0%	*.199*^{E}
Apgar score 5 min	4-6: 14.3% 7-10:85.7 %	4-6:0% 7-10: 100%	*.502*^{E}	4-6: 0% 7-10: 100%	*.071*^{E}
Hollingshead SES (SD)	37.6 (6.2)	39.4 (9.6)	*.374*	39.7 (8.4)	*.372*

p^a:paired samples t-test
p^b:ANOVA
Nominal data: χ^2 with Exact test $^{(E)}$

Table 2. *Hospitalization characteristics*

	UVH Patients	BiVH Patients
Mean age initial surgery, y:m (SD)	.07 (.06)	1.5 (1.9)
Mean weight first surgery, gr (SD)	3655(1004)	8591(5822)
Hospital stay (lifetime – days)	39 (28-48)	7 (7-9)
ICU stay (lifetime – days)	8 (7-11)	2 (1-3)
Duration surgery (lifetime – minutes)	565 (447-716)	125 (105-170)
Duration ECC (lifetime – minutes)	192 (140-280)	56 (41-69)
Duration Clamp (lifetime – minutes)	81 (48-110)	33 (26-44)
Duration anesthesia (lifetime – minutes)	835 (685-1008)	230 (205-255)
Intubation Duration (lifetime – minutes)	5555(2698-7610)	705 (384-1560)

Age and weight at first intervention are expressed as mean (SD)
Medical characteristics are expressed as Median (IQR)
Mann-Whitney (Exact)
**p<.01

Table 3. *Neuropsychological performance*

	UVH patients	*UVH controls*	p[a]	*Adj. p*	*Effect size* d / r	*BiVH patients*	pb‡	*Adj. p*	Effect size d / r
N	17	17				46			
WISC-III-NL									
Estimated full scale IQ	101.1±13.5	107.8±12.2	*.288*	.460	.52	102±13.6	*.175*	.511	.06
Similarities	11.6±2.4	12.2±2.4	*.608*	.634	.25	12.1±2.7	*.335*	.766	.19
Picture arrangement	9.5±2.8	10.7±2.6	*.244*	.488	.44	9.4±3	*.080*	.511	.03
Block Design	10.3±2.6	11.6±2.9	*.293*	.468	.47	9.9±2.9	*.878*	.952	.14
Vocabulary	9.4 ±2.8	10.5±2.5	*.496*	.566	.41	9.9±2.3	*.178*	.511	.20
NEPSY-II-NL									
Auditory Attention and Executive Functioning									
Auditory Attention pc	50(25-75)	75(75-75)	*.016**	.133	.42	75(50-75)	*.086*	.602	.21
Response Test pc	50(17.5-50)	50(37.5-75)	*.047**	.164	.42	50(25-50)	*.526*	.838	.09
Design Fluency	9.1±2.6	10.8±2.4	*.024**	.030*	.67	9.4±2.1	*.538*	.824	.12
Inhibition pc	50(25-75)	50(50-75)	*.176*	.308	.25	50(50-75)	*.509*	.838	.09
Inhibition time	9.5 ±3.6	11.2±1.9	*.098*	.336	.59	9.6±1.9	*.129*	.511	.03
Language Domain									
Comprehension of Instructions	10.5±2.3	12.1±3	*.136*	.375	.59	10.7±2.8	*.380*	.766	.07
Repetition of Nonsense Words	11±3	11±2	*1.0*	1	0	9.7±2.3	*.483*	.824	.48
Speeded Naming									
Total pc	25(25-75)	50(25-62.5)	*.344*	.535	.19	25(25-50)	*.976*	.976	0
Speeded naming time pc	75(75-75)	75(75-75)	*1.0*	1	.17	75(75-75)	*.677*	.861	.04
Word Generation									
Semantic	9±2.7	9.9±3.1	*.414*	.496	.31	9.3±2.3	*.535*	.824	.12
Linguistic pc	50(25-62.5)	50(37.5-62.5)	*.391*	.547	.21	25(10-50)	*.509*	.838	.10
Memory and Learning Domain									
Memory for Faces	9.4 ±3.3	10.6±2.6	*.157*	.375	.40	9.8±2.6	*.013**	.511	.13
Delayed	10.8 ±3.5	11.4±2.5	*.524*	.571	.19	10.7±3.6	*.142*	.511	.02
Memory for Names	8.4 ±2.9	9.2±2.4	*.342*	.456	.30	9±2.5	*.820*	.952	.22
Narrative Memory	10.2 ±2.1	11±1	*.154*	.375	.48	11±2	*.127*	.511	.39
Cued recall pc	50(25-75)	75(50-75)	*.033**	.154	.39	50(25-75)	*.676*	.861	.05
Word List Inference									
Working memory	11.7 ±2.2	10.6±1.7	*.252*	.465	.56	10.2±1.9	*.776*	.952	.73
Word recall	11 ±1.7	11.8±2.2	*.406*	.512	.40	11.3±2.3	*.212*	.541	.14

Standard scores: mean (SD);Pc-scores: median (IQR)
a:Paired T-test & Wilcoxon signed rank test
b:ANOVA & Mann-Whitney U test (Exact)
‡gender was added as covariate in ANOVA
*p<.05 , **p<.01

Table 3. *Neuropsychological performance*

	UVH patients	*UVH controls*	p[a]	*Adj. p*	Effect size d / r	*BiVH patients*	p[b]‡	*Adj. p*	Effect size d / r
Sensorimotor Domain									
Imitating Hand Positions	9.6±1.8	10.5±1.7	*.172*	.375	.47	9.2±2.5	*.589*	.842	.18
Manual Motor Sequences	11.2 ±3	12.9±1.3	*.051*	.232	.73	11.4±3.2	*.952*	.952	.06
Fingertip Tapping	8.4±1.7	9.9±1.9	*.018**	.030*	.83	-	-		-
Visuomotor Precision									
Time pc	50(25-62.5)	75(50-75)	*.124*	.347	.29	50(25-75)	*.518*	.838	.08
Error pc	25(10-37.5)	25(5-50)	*.946*	1	.01	25(10-50)	*.539*	.838	.07
Social Perception Domain									
Affect Recognition pc	10±(10-50)	25(6-50)	*.145*	.290	.25	17.5(4-50)	*.885*	.953	.01
Theory of Mind									
Verbal Task	11.2±2.7	12±2.7	*.316*	.474	.29	10.5±2.6	*.170*	.511	.26
Contextual Task	10.4±2.3	11±2	*.322*	.454	.27	9.8±2.5	*.400*	.766	.25
Visuospatial Processing Domain									
Block Construction	10.4 ±2.5	12.5±2.3	*.058*	.232	.87	10.4±2.2	*.909*	.952	0
Design Copying pc	10(3.5-10)	10(10-25)	*.019**	.133	.39	10(2-25)	*.869*	.953	.02
Motor	9.8 ±2.3	12.3±1.8	*<.001***	<.001	1.2	9.2±2.9	*.923*	.952	.22
Global pc	25(7.5-37.5)	25(10-50)	*.125*	.290	.27	25(10-50)	*.422*	.838	.10
Local	7.7 ±1.9	9.6±1.3	*.002***	.024*	1.1	7.8±2.1	*.623*	.842	.05
Geometric Puzzles pc	50(25-75)	50(25-75)	*.809*	.943	.05	50(25-50)	*.149*	.695	.18
Route Finding pc	50(25-50)	50(25-50)	*.688*	.875	.09	25(10-25)	*.035**	.049*	.26

Standard scores: mean (SD);Pc-scores: median (IQR)
a:Paired T-test & Wilcoxon signed rank test
b:ANOVA & Mann-Whitney U test (Exact)
‡gender was added as covariate in ANOVA
*p<.05 , **p<.01

Table 4. *Behavioral functioning: CBCL*

CBCL	*UVH patients*	*UVH Controls*	p[a]	*Adj. p*	*Effect size* r	*BiVH patients*	p[b]‡	*Adj. p*	*Effect size* d
N	17	17				46			
	Mean (SD)	Mean (SD)				Mean (SD)			
Composite Problem behavior scales									
Internalizing	55.9±8.7	48.7±10.6	*.056*	.074	.32	52.8±9.6	*.480*	.480	.33
Externalizing	52±10.1	47.1±9.2	*.017**	.034*	.41	49.1±9.7	*.309*	.412	.29
Total problem score	53.9±8.7	47.3±10.3	*.013**	.034*	.42	51.8±9.1	*.179*	.358	.23
Total competence	42.4±11.8	46.3±8.7	*.351*	.351	.16	42.4±8.4	*.109*	.358	0
Competence scales									
Special education(%)	Yes:11.8 No:88.2	Yes: 0 No: 100	*.485[E]*			Yes:8.7 No:91.3	*1.0[E]*		
Repeating school year(%)	Yes:11.8 No: 88.2	Yes: 0 No: 100	*.485[E]*			Yes:13 No:87	*1.0[E]*		
School problems(%)	Yes: 47.1 No: 52.9	Yes:11.8 No: 88.	*.024χ²**			Yes:32.6 No: 67.4	*.290χ²*		

p[a] :Wilcoxon Signed Rank Test
p[b]: ANCOVA
χ^2 test (Fishers Exact test [E])
‡gender was added as covariate in ANOVA
*p<.05

DISCUSSION

Univentricular physiology represents the severe spectrum of CHD and constitutes ~2% of all (CHDs)[1]. This multicenter study presents an up-to-date evaluation of neurobehavioral outcome in children treated for UVH at a mean age of 9 years, aiming to extend knowledge on long-term development of these children after completion of staged palliation.

From a neuropsychological viewpoint, UVH patients are doing relatively well when compared with healthy controls. Full estimated IQ scores were found to be in normal ranges for the majority of the UVH patients, corroborating previous findings[6, 7, 20, 21], but contradicting other results[4]. In the latter study, the UVH cohort had a particularly long hospital stay after the Norwood procedure (median 25 days) or heart transplant (median: 46 days), which correlated negatively with intelligence. In our study, only attentional scores were found to be associated with lifetime ICU stay. This might suggest that children, who experienced an eventful postoperative course, with prolonged mechanical ventilation and subsequent longer ICU stay, are the ones that perform poorly during neuropsychological assessment.

In addition to an intelligence screening, we also assessed a comprehensive neuropsychological test battery, with encouraging outcomes. When compared with age- and gender-matched controls, UVH patients showed similar neuropsychological outcomes. Despite optimistic scores for several neuropsychological domains, results indicated subtle deficiencies in auditory sustained and alternating attention, fine motor skills, visuospatial information processing, and to a lesser extent, memory performance. Effect sizes indicated clinically meaningful differences.

Shortcomings in attention regulation, processing speed and impulse control may influence general school functioning as attention is essential for each cognitive and motor task. UVH survivors seem to be at a disadvantage for these cognitive skills, demonstrated by recent research[9] and the current results. Attentional problems have been described in a sample of 7 HLH patients in ~57% of patients, and for other UVH lesions (n = 19) in up to ~53%[22].

Deficient gross and fine motor functions are among the most described long-term outcomes after complex cyanotic CHD repair[8-10]. UVH patients in the current study displayed inefficient eye–hand coordination, motor programming and deficient tactile/kinesthetic information processing when performing fingertip tapping and rhythmic manual motor sequences. Central nervous system anomalies and ongoing perioperative hypoxemia in UVH patients may affect the developing

young brain[23]. Moreover, reduced total brain volume, including deviant white matter development, are suggested to be accountable for deficient motor functioning[24]. It remains uncertain if these patients suffered from mild covert neurological injury due to ongoing insufficient systemic blood flow and multiple interventions to explain the current findings. The cause and location of brain regions that are particularly vulnerable for delayed/altered development and ongoing hypoxemia remain to be determined.

Impaired visuospatial skills have been found consistently among complex CHD populations[8-10, 25]. Our results suggest a continuity of these problems throughout childhood. It has been postulated that complex visuospatial tasks pose a specific challenge for children with CHD, and impaired visual–perceptual abilities are thought to explain poor performance[25]. Pronounced reduced hippocampal volume (>8% when compared with controls) in cyanotic CHD patients without overt lesions have been found to correlate with perceptual reasoning task scores[24]. This region may be particularly vulnerable to the chronic hypoxemia and (post-) operative events these children are exposed to. It remains unclear in what way these cognitive difficulties in attention, motor skills and visuospatial information processing persist and evolve throughout adolescent life and affect or hamper school choice, sports engagement and future career options.

Only few differences were found in long-term neurobehavioral functioning in UVH patients or BiVH patients. These differences were accompanied by small-to-medium effect sizes. Previous studies demonstrated that intellectual and neuropsychological functioning between cyanotic or acyanotic CHD is comparable[2, 8, 9, 24]. With respect to behavior, parents report that UVH patients are burdened with more externalizing and total problem behavior, suggesting that patients have difficulty in regulating their behavior and may display aggressive, hyperactive, non-compliant and undercontrolled behavior (e.g. disobedience, impulsivity and swearing), corroborating previous research[8]. Parents also indicated a higher frequency of school problems when compared with controls. Repeating a grade was reported in ~12% of the UVH group. The internalizing problem score verged on significance, suggesting that some of these children are also burdened with anxious, depressive and overcontrolled behavior (e.g. fearfulness, headaches, social inhibition and worry), ratifying other results[3, 8] . Remarkably, parents of UVH and BiVH patients display similar rates of repeating a grade (12% and 13%),

suggesting that school problems are also evident in the latter diagnostic group. Problems in emotional regulation can be considered as the common denominator for behavioral issues. This might manifest in poor self-regulation (e.g. irritable negative emotional tone and poor adaptability) and subsequent attention deficiencies[3]. In addition, the protective and overly concerned nature of parenting may have caused behavior to deviate from the norm.

Awareness should be raised in teachers too, because these behavioral manifestations may be mistakenly considered symptoms relating to Attentional Deficit Hyperactivity Disorder.

It is noteworthy that neuropsychological performance of children and behavioral ratings by parents of those who required aortic arch reconstruction for HLH did not differ significantly from those who had staged surgical repair for TA. This validates previous research efforts that showed intellectual, motor outcome and behavior between HLH and other UVH lesions to be quite similar[3, 6, 10]. These results shed a different light on the theory that, in HLH patients, prenatal brain injury occurs through diminished cerebral and aortic perfusion as their long-term outcomes are equivalent to those with an underdeveloped or absent right ventricle.

Our positive findings are somewhat surprising given multiple and long hospitalizations, consecutive periods of cardiopulmonary bypass with deep hypothermic cardiac arrest in the surgical management and chronic hypoxemia in UVH patients. Associations with these parameters and cognitive outcome have been highlighted in previous research[4, 5].

Other known etiological considerations pertaining to adverse neuropsychological functioning in CHD patients imply altered cortical brain development[26], the high frequency of genetic anomalies[5, 12] and low parental education or socio-economic status[5, 21].

The fairly good neuropsychological results of our patients should be observed in light of the general healthy condition of these children. Our UVH patients were born at term gestational age, had normal birth weight and had no known or suspected genetic abnormalities, developmental syndromes or neurological diagnoses. The former are innate elements for a rather smooth development.

Other studies showed that the latter factors comprise certain risks for poor long-term cognitive outcome[3, 5]. Cumulative time of ICU stay and mechanical ventilation was associated with long-term developmental outcome. These factors may reflect an eventful postoperative course and intensified ICU monitoring in

subsamples of our patients. Intrinsic characteristics such as pregnancy duration, birth weight and SES were also found to influence long-term cognitive development. Other research has promoted delayed elective delivery to 39–40 weeks to improve birth weight[5], but the negative relation between cognitive outcome and pregnancy duration in the current study suggests cumulative intrauterine impact of adverse fetal circulation. It is very challenging to find a balance in improving outcome scores by modifying these factors.

Hoskoppal et al.[2] showed that neurodevelopment in UVH children is improving, on the premise that they are non-syndromic. Pre- and postoperative neurological injury, specifically ischemic insults, occurs often in complex CHD populations[22, 24]. Brain plasticity is plausibly an important factor in countering early ischemic injury before and after staged palliation that occurs in critical periods of neurological development, warranting the preservation of certain higher cognitive functions.

In addition, it is possible that parents of these patients are now highly attentive to possible cognitive problems and seek early consulting services, anticipating cognitive delay. Nevertheless, clinicians and parents share responsibility in addressing and signaling school functioning during the follow-up visits for early identification of high-risk conditions.

Limitations of this study include the retrospective rather than longitudinal study design, lack of neuroimaging data and small sample size of the UVH group. The power of the study was limited because of sample size. The power to detect a difference in full scale estimated IQ, for example, was 36%. The sample size required to achieve power of 80% would have been 53 participants for each sample separately. In addition, population-based Dutch norms for the NEPSY-II-NL might be rather low for our study group of Belgian children, overrating performance and possibly missing clinically meaningful observations.

CONCLUSION

With increasing perioperative survival in children with complex CHD, greater emphasis is placed on neurodevelopmental comorbidity and behavioral outcome of children palliated for severe CHD. Over the last years, surgical techniques and postoperative management have changed significantly. UVH patients undergoing staged palliation nowadays have different outcomes compared with children having the same treatment a few decades ago. Our results suggest that adverse

neurodevelopmental outcome in school-aged children treated for UVH is less compromising than expected in the current era of surgical palliation. All outcome scores were within normal ranges. Subtle shortcomings in attention, fine motor skills and visuospatial information processing characterize the neuropsychological profile of UVH patients. These children were also found at risk for internalizing and especially externalizing problem behavior and more school problems by parental reports.

It becomes advisable to screen UVH and BiVH patients during the follow-up visits using short questionnaires and identify those at greater risk for cognitive and/or behavioral problems. In this way, specific longitudinal patterns can be observed. Tailored referral for a comprehensive neuropsychological evaluation could be implemented, promoting improved developmental trajectories.

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CHAPTER 7

BEHAVIORAL AND EMOTIONAL OUTCOMES IN SCHOOL-AGED CHILDREN FOLLOWING INVASIVE TREATMENT FOR CONGENITAL HEART DISEASE: A MULTICENTER EXPERIENCE

Sarrechia I., Miatton M., François K., Gewillig M., Meyns B., Vingerhoets G., & De Wolf D. *Behavioral and emotional outcomes in school-aged children following invasive treatment for congenital heart disease: a multicenter experience* (Submitted Manuscript)

ABSTRACT

Objective
To assess the occurrence of behavioral and emotional problems at school age using parental reports after surgical or catheter-based treatment for various forms of congenital heart disease (CHD) in infancy.

Methods
This study presents a multicenter cross-sectional observational investigation, parents of 94 CHD patients and 94 matched healthy control children, aged 6-12 at time of recruitment, completed a questionnaire on cognitive and emotional functioning and the Child Behavior Checklist-6/18.

Results
Parents of CHD patients reported significantly more problems in attention, fine and gross motor skills, and anxiety compared to parents of healthy controls on the cognitive and emotional questionnaire. On the CBCL, parents of patients reported significantly higher problem scores for the scales withdrawn/depressed behavior, somatic complaints, social problems, thought problems, aggressive problems, affective problems, anxiety problems post-traumatic stress symptoms, internalizing, and total problems compared to the reference group. CHD parents also indicated reduced school performance, higher proportions of their children needed special education, repeated a school year and experienced school problems.

Conclusion
Overall, although modern medical management of CHD has excellent functional results, parents of patients reported persisting higher levels of behavioral and emotional problems compared to parents of a matched control group. Assessing psychosocial adjustment in children treated for CHD can be helpful to detect children at higher risk for academic underachievement and possible psychopathology.

Keywords
Congenital Heart Defect • behavioral functioning • emotional outcomes

INTRODUCTION

Over the past decades, surgical and transcatheter management of congenital heart disease (CHD) has changed dramatically, resulting in improved survival rates[1]. At the same time, this trend gave rise to growing concern regarding neurodevelopmental and psychosocial comorbidity. It is well documented that a significant proportion of school-age survivors of infant cardiac surgery suffer from adverse neurodevelopmental sequelae. Although intellectual capacities are relatively preserved and in normal ranges[2, 3], a few at-risk neurocognitive domains have been identified that could hamper school competence. Subtle deficiencies in attention, visuospatial information processing and predominantly suboptimal motor skills characterize the neuropsychological profile of school-aged patients treated for CHD[2, 4, 5]. With the growing number of CHD survivors, more children treated for CHD are estimated to require remedial services, such as special education, physical, occupational and speech therapy[3-7]. Furthermore, a higher than normal pattern of problematic behavior such as anxious, depressive, and overcontrolled behavior (internalizing problem behavior) or disruptive, aggressive, hyperactive, noncompliant, and undercontrolled behavior (externalizing problem behavior), but also impaired socialization skills have been described in this patient population[8-10]. Despite improved peroperative management and cardiothoracic surgical techniques, this seems to be a consistent and persisting finding over time[11]. Studies exploring possible medical predictors for long term behavioral issues have shown only marginal effects[12] and mechanisms underlying this late morbidity are incompletely understood.

The purpose of this study was to explore and update parental views on behavioral and emotional problems in non-syndromic children treated for various forms of CHD in infancy in the current surgical era, and study potential differences among patient groups presenting with different complexity of and treatment for CHD. Behavioral and emotional functioning was assessed using a questionnaire on cognitive skills and emotional functioning, and the Child Behavior Checklist (CBCL). The latter parent-report measure of emotional and behavioral problems contains categories adhering to experts' based Diagnostic and Statistical Manual of Mental Disorders (DSM) classification and allows to stratify the risk of psychopathology in clinical populations[13].

METHODS

Participants

This study is part of a multicenter follow-up project on neurobehavioral outcomes in children with various forms of congenital heart defect[14-16]. Patients with various types of CHD, treated at Ghent University Hospital and University Hospital Gasthuisberg Leuven between 1998 and 2012 were invited to participate and were recruited from 2011 through 2013. Both institutions' medical ethics committees approved the study and parental written consent was obtained for each child enrolled. Exclusion criteria for the patients diagnosed with univentricular heart defect (UVH) were defined as severe genetic abnormalities, developmental syndromes and cerebral palsy. Patients treated for biventricular heart defect (BiVH) were excluded if there was a history of perinatal problems, preterm gestational age (<37 weeks), birth weight <2000g, genetic abnormalities or developmental syndromes. Patients files were screened for eligibility and out of 175 invited parents of patients, 94 (~53%) responded positively to our appeal and participated. Response rates were 68% (17/25) and 51% (77/150) for UVH and BiVH patients respectively. Reasons for non-participation included developmental delay (5%), prematurity (7%), family issues (2%) and no response at all (33%).

The UVH cohort underwent staged surgical palliation between 2000-2009. HLHS patients treatment was initialized with the Norwood operation and concluded with the Fontan circulation. TA patients had an initial pulmonary artery banding and a last total cavopulmonary connection (TCPC) operation. Patients with a BiVH defect were treated during 1999-2010 with one single open-heart surgery with mild-to-moderate hypothermic (25°C–37°C) cardiopulmonary bypass.

For every patient, more than one healthy control child was approached through primary schools and their parents if gender, age and parental educational level (if provided) were similar. These parents were invited to participate, and resulted in a total response rate of ~75%. All enrolled children attended school full time and did not experience any physical restrictions, nor had any developmental problems as reported by their parents.

Parents were asked to complete several questionnaires regarding behavior, cognition, and psychosocial well-being of their offspring as part of a large cross-sectional project to evaluate the neurodevelopmental and behavioral outcomes of

children treated for CHD compared to children without significant medical history and assumed to have a normal developmental trajectory. While the children underwent formal neurodevelopmental assessment, parents filled in the questionnaires and returned them afterwards or by postal mail. Feedback was provided by the developmental neuropsychologist (I.S.) if requested.

Measures

Questionnaire on cognitive skills and emotional functioning. This questionnaire was originally constructed by Newman et al.[17] to rate adult subjective complaints after coronary artery bypass surgery and was adapted before in another similar study regarding cognitive functioning and emotional well-being of CHD patients as rated by parents[10]. We extended the aforementioned questionnaire with additional questions on emotional well-being and anxiety issues. We also grouped together the sometimes/mostly classification into one category (occasionally). All parents enrolled in the current study were asked to complete a survey on various aspects of cognitive and emotional functioning. The questionnaire included 22 statements or questions regarding attention (sustained and divided), memory (recall and learning), problem solving strategies (planning and executing), and motor functioning (fine and gross motor skills). Items were rated on a three-point Likert scale (never – occasionally –always). Analyses showed satisfactory internal consistency for this questionnaire (Cronbach's alpha = 0.87).

Behavioral functioning. The Dutch version of the Achenbach Child Behavior Checklist for Children aged 6 to 18 (CBCL-6/18)[13] was completed by parents of each child to obtain standardized measures of various aspects of behavioral, social, and emotional functioning. The frequency of common behavior problems are rated on 113 questions with a Likert-scale construction (0=absent, 1= occurs sometimes, 2=occurs often). These questions reveal information about eight empirically based scales: withdrawn/ depressed behavior, anxious/depressed behavior, social problems, thought problems, attention problems, rule breaking behavior and aggressive behavior. These eight scales cluster into corresponding composite scales: internalizing behavior problems, externalizing behavior problems and total behavior problems. The 113 questions also target 9 empirically derived *DSM-IV* scales; Affective problems, somatic problems, attention/hyperactivity problems, oppositional defiant problems, conduct problems, sluggish cognitive tempo, obsessive/compulsive problems, and post-traumatic stress disorder (PTSD)

symptomatology. Outcome scores are expressed as T-scores (mean = 50, SD = 10) and are based on norms for corresponding gender and age. The instrument has been reported to have excellent psychometric properties; inter-rater reliability with intra-class correlations ranging from .93 to .96 for the 118 items, test-retest reliability between .95 and 1.00 for the competence and problem items respectively, and internal consistency of .78-.97[13].

The Hollingshead Four Factor index[18] rated socio-economic status (SES). This index calculates an estimate of social status using educational and occupational information.

Statistics

Data were analyzed using SPSS version 22.0 statistical Package (SPSS, Inc., Chicago, IL, USA). Normality of the data was checked with Kolmogorov-Smirnov tests. Categorical variables were expressed as proportions and Chi-square (with Fisher's Exact, Bonferroni corrected) was employed to explore group differences. Odds ratio was added as a measure of effect size (measure of association between an exposure and outcome). We considered OR = 1.68, 3.47, and 6.71 are equivalent to Cohen's d effect size = 0.2 (small), 0.5 (medium), and 0.8 (large), respectively[19] When CBCL scale scores were distributed normally, data was handled in a parametrical manner using MANOVA. When criteria for normality were not reached, Mann-Whitney U tests were performed to study group differences. We adjusted for multiple testing correction with the False Discovery Rate[20]. For parametric data, Cohen's d (using pooled variance) was computed (composite scales), for data that did not meet normality assumptions (sub scales), effect sizes for Mann-Whitney, r, were calculated. Classification was as follows; small (d= .20/r=.10), moderate (d= .50/r= .30), large (d= .80/r=.50) and very large (d = 1.3/r = .70).

RESULTS

The CHD cohort consisted of 94 children with various forms of CHD. Table 1 gives an overview of patient- and treatment characteristics. The age at first intervention ranged from 0 to 8 years, depending on diagnosis (UVH or BiVH) and treatment (surgery or catheter). Mean age at first intervention for the UVH cohort was 27 days (SD 24 days), and 2 years 5 months (SD 2 years 2 months) for the BiVH cohort. Mean age at time of recruitment for patients was 9 years 1 month (SD 2 years and 3 months). Due to matching efforts, no significant differences were found between the patient group and control group on gender distribution, age at testing, and socio-economic status. The latter variable ranged from 24 to 66, with higher scores reflecting higher SES. Demographics and CHD diagnoses and treatment characteristics can be found in Table 1.

Questionnaire on Cognitive Skills and Emotional Functioning

A significant higher proportion of patients' parents reported problems in subareas of attention, memory, problem solving skills, motor functioning, emotional well-being, and more anxiety compared to parental reports of matched controls. These significances are flanked by small-to-medium effect sizes as revealed by odds ratio (range 1.89 – 5.35), suggesting clinical relevancy. Table 2 displays the questionnaire and parental ratings. Statistical analysis revealed that parents of patients treated for UVH noticed significantly more problems in fine and gross motor functioning than parents of patients treated for BiVH ($p < .01$). These results should be interpreted with caution since power calculations revealed that the minimal sample size for each group separately should consist of 50 patients to achieve power of .80.

Behavioral Functioning

Parental reports on problem behavior and competence revealed various significant group differences, listed in Table 3. Parents of patients rated more problems in withdrawn/depressed behavior ($p < 0.05$), somatic problems ($p < 0.05$), social problems ($p < 0.01$), thought problems ($p < 0.01$), and aggressive behavior ($p < 0.01$) compared to the reference group. These scores resulted in significant group differences on the composite scales, internalizing behavior problems ($p < 0.01$), and total problem behavior ($p < 0.01$). DSM-oriented scale ratings showed more affective problems ($p < 0.05$), anxiety problems ($p < 0.05$), and symptoms adhering to PTSD ($p < 0.001$). Parents of patients also signaled

significantly lower school competence compared to parents of matched controls. Higher proportions of patients' parents reported extra need for special education ($p < 0.05$), a higher frequency of repeating a school year ($p < 0.01$) and more school problems ($p < 0.001$). Multiple testing correction discarded some of the statistical significant findings. Nevertheless, we stress the clinical relevance of the current results. Effect sizes indeed ranged from small to medium (d: 0.26-0.45/ r:0.15-0.26), suggesting clinical meaningful implications.

Table 1. *Demographics and medical characteristics*

	CHD patients	Controls	*p*
N	94	94	
Sex	♂:45 ♀:49	♂:45 ♀:49	*ns*χ^2
Age at assessment, mean (SD)	9y1m±2y3m	9y1m±2y4m	.973
SES, mean (SD)	40 (8)	42.1 (7.8)	.080
	Treatment		
Biventricular CHD (BiVH)	Surgery Catheter		
Atrial septal defect	18 (19.1%) 30 (31.9%)		
Ventricular septal defect	29 (30.9%)		
Univentricular CHD (UVH)			
Tricuspid valve atresia	9 (9.6%)		
Hypoplastic left heart	8 (8.5%)		
Number of interventions, mean (range)	1.4 (1-4)		
Age at first treatment, mean (range) [years]	2y1m (0-8)		
Weight at first treatment, mean (range)[kg]	10.8 (2.4-28)		
Total lifetime hospital stay, mean (range) [days]	12.7 (1-78)		
Total lifetime ICU stay, mean (range) [days]	5 (1-30)		

χ2- test (Fisher's Exact ^{E})
ICU-intensive care unit

Table 2. *Response pattern parental cognitive and emotional questionnaire*

1. Cognition		CHD (N=94)	Controls (N=94)	P	Odds Ratio (C.I. 95%)
Attention					
My child has problems keeping attention focused for a long time (f.i. when watching television or playing games)	Never Occasionally Always	37.2% 61.7% 1.1%	53.8% 46.2% 0%	.032*[E]	1.96 (1.09-3.53)
My child has problems sustaining mental work (f.i. when studying)	Never Occasionally Always	36.2% 58.5% 5.3%	34.1% 65.9% 0%	.080[E]	.911 (0.49-1.66)
To perform well, my child has to work slower than peers	Never Occasionally Always	56.4% 37.2% 6.4%	73.6% 26.4% 0%	.006**[E]	2.15 (1.16-4.01)
My child has problems doing two tasks simultaneously	Never Occasionally Always	34% 60.6% 5.3%	42.9% 56% 1.1%	.155[E]	1.45 (0.80-2.63)
My child is highly distractible	Never Occasionally Always	19.1% 74.5% 6.4%	20.9% 74.6% 4.4%	.863[E]	1.11 (0.54-2.29)
My child reacts slower to questions or situations than peers	Never Occasionally Always	66% 33% 1%	80.2% 19.8% 0%	.038*[E]	2.09 (1.07-4.88)
Memory					
My child is forgetful (f.i. forgets to do homework, forgets necessary school material)	Never Occasionally Always	47.9% 50% 2.1%	49.5% 49.5% 1.1%	*ns*	1.06 (0.59-1.89)
My child cannot remember certain events or assignments	Never Occasionally Always	72.3% 26.6% 1.1%	75.8% 24.2% 0%	.800[E]	1.19 (0.62-2.31)
My child has problems learning new information (f.i. summaries)	Never Occasionally Always	61.7% 38.3% 0%	76.9% 23.1% 0%	.027*[E]	2.06 (1.09-3.92)
Problem solving skills					
My child has problems planning activities	Never Occasionally Always	59.6% 40.4% 0%	61.5% 38.5% 0%	.785	1.08 (0.60-1.95)
My child has problems with decision making	Never Occasionally Always	35.1% 63.8% 1.1%	38.5% 61.5% 0%	.761[E]	1.15 (0.63-2.10)
When a task demands multiple steps, my child has problems determining the order of the steps	Never Occasionally Always	44.7% 54.3% 1.1%	76.9% 23.1% 0%	<.001**[E]	4.12 (2.18-7.78)
2.* Motor *functioning					
Fine & gross motor skills					
The handwriting of my child is less legibly than that of peers	Never Occasionally Always	48.9% 45.7% 5.3%	58.2% 37.5% 3.3%	.456[E]	1.45 (0.81-2.60)
My child has problems with fine motor tasks (f.i. cutting straight, coloring, threading beads)	Never Occasionally Always	66% 29.8% 4.3%	91.2% 8.8% 0%	<.001**[E]	5.35 (2.30-12.42)
My child has problems with gross motor tasks (f.i. swimming, running, gymnastics)	Never Occasionally Always	61.7% 31.9% 6.4%	86.8% 12.1% 1.1%	<.001**[E]	4.08 (1.95-8.53)

3. Emotional functioning					
Emotional functioning					
My child is irritable / short-tempered	Never Occasionally Always	29.8% 69.1% 1.1%	39.6% 59.3% 1.1%	.550[E]	1.54 (0.83-2.83)
My child has significant mood swings	Never Occasionally Always	48.9% 51.1% 0%	64.8% 35.2% 0%	.029*	1.92 (1.06-3.47)
My child is sad / depressed	Never Occasionally Always	50% 50% 0%	78% 22% 0%	<.001**	3.55 (1.87-6.73)
Anxiety					
My child is generally anxious	Never Occasionally Always	59.6% 40.4% 0%	73.6% 26.4% 0%	.043*	1.89 (1.01-3.52)
My child worries about his/her health	Never Occasionally Always	58.5% 41.5% 0%	79.1% 20.9% 0%	.003**	2.68 (1.40-5.15)
My child is restless	Never Occasionally Always	52.1% 47.9% 0%	65.9% 33% 1.1%	.051[E]	1.77 (0.98-3.21)
My child has problems sleeping	Never Occasionally Always	70.2% 28.7% 1.1%	82.4% 16.5% 1.1%	.107[E]	1.98 (0.98-3.99)

χ2- test (Fisher's Exact [E])
*p<.05

Table 3. *Behavioral functioning as measured by parental CBCL-6/18 (Dutch version) responses*

CBCL **N**	CHD 94	Controls 94	F [df]	p	Adj. p	Effect Size *d/r*
Problem behavior Scales	Mean±SD	Mean±SD				
Withdrawn / depressed	55.8±7	53.8±5.5		.033*	.073	.15
Somatic complaints	56.2±6.7	54±5.2		.028*	.070	.16
Anxious/ depressed	54.5±5.6	54.2±6		.139	.198	.01
Social problems	55±5.7	52.9±4.5		.003**	.005**	.21
Thought problems	56.4±6.7	53.7±5.7		.001**	.005**	.24
Attention problems	55.2±6.2	53.4±4		.074	.123	.13
Rule breaking behavior	53±4.3	52.4±4.3		.224	.277	.09
Aggressive behavior	54.3±5.8	52.7±5		.008**	.040	.19
Composite Scales						
Internalizing	53.4±9	49.5±9.5	7.7 [1]	.006**	.012*	.41
Externalizing	49.4±9.8	46.7±9.1	3.5 [1]	.060	.080	.26
Total problem score	51.9±9.3	47.6±8.9	10.5 [1]	.001**	.004**	.45
DSM-Clinical scales						
Affective problems	56.7±6.6	54.7±6		.023*	.065	.16
Anxiety problems	55.8±6.4	53.9±5.3		.012*	.048*	.18
Somatic problems	56.2±7.2	54.3±5.7		.070	.127	.13
Attention/Hyperactivity problems	54.3±5.3	53±4.5		.112	.172	.11
Oppositional Defiant problems	54.3±5.3	52.8±4.2		.068	.123	.13
Conduct problems	53.3±5.2	52.5±4.8		.236	.277	.08
Sluggish cognitive tempo	54.8±6.5	53.2±4.4		.285	.316	.07
Obsessive/Compulsive problems	55.6±7	54.4±6.5		.155	.206	.10
Post-Traumatic Stress problems	56.9±6.6	53.7±6		<.001**	<.001**	.26
Competence scales						
Activity	39.9±8.8	39.3±9.2		.534	.562	
Social	48.5±8.6	49.5±6		.856	.865	
School	46.7±8.8	43.8±8.8		.020**	.065	
Special education	Yes: 7.4%	Yes: 0%		.014*^{E}		
Repeating school year	Yes: 12.8%	Yes: 1.1%		.002**		
School problems	Yes: 34%	Yes:12.1%		<.001**		
Total competence	43.6±9.5	43.9±8.8	.029 [1]	.865	.865	.02

Subscales: Mann-Whitney U test (Exact); composite scales: MANOVA
Nominal data: χ2- test (Fisher's Exact ^{E})
*p<.05 , **p<.01

DISCUSSION

The primary objective of this study was to investigate and update parental views on the occurrence of behavioral, cognitive, and emotional problems in children that were treated in infancy and early childhood for varying forms of CHD by the time they reached school-age (6-12 years).

We used a formerly validated questionnaire[10] to explore parent's perceptions of attention, memory, problem solving, motor skills, and emotional functioning of their children. Parents of patients reported problems within each domain addressed. Significant higher proportions of patients' parents indicated higher frequencies of problems in sustained and divided attention compared to parents of healthy controls. They also report that working speed and reaction processes appear to be slower in their children compared with peers. Questions addressing memory revealed that patients are not forgetful, nor have they problems with remembering events or assignments. They do however, have problems with learning new information (e.g. remembering contents from a recent class). Patients display more difficulties with the execution of complex tasks that consist of multiple steps, while planning and decision making appear to be normal. Parents of our patient cohort rated motor skills to be lower than peers in terms of fine motor tasks involving adequate eye-hand coordination (cutting straight, threading beads), but also gross motor functions (running, gymnastics). Handwriting appears to be unaffected.

These results are in line with data reported in a previous study[10] where problems in sustained and divided attention, memory and learning, problem solving, and gross motor tasks were apparent. This leads us to conclude that seven to ten years later, still the same aspects are notable in CHD cohorts, irrespective of late advancements in peroperative care.

A higher percentage of parents in the CHD-group indicated problems in the emotional spectrum, mood swings and a depressed, sad mentality are common among these children. General anxiety and worries regarding their own health are frequently seen in CHD children when compared to ratings of control parents.

Parental reports did not reveal any differences between patients and controls regarding activity participation, or social competence (number of friends and the frequency of spending time with them) on the CBCL items regarding overall competence. On the other hand, patients' parents reported reduced school

performance, a higher percentage of patients requiring special education, repeating a school year and experiencing general school problems. These findings corroborate with earlier studies that these patients experience more academic problems and more often require educational and therapeutic support[3]. Shillingford and colleagues reported that, in a cross-sectional analysis of school-aged patients (mean age ~8 years) who underwent neonatal cardiac surgery for CHD, 49% received some form of remedial academic services, and 15% were assigned to a special-education classroom[6]. In addition, the 16-year follow-up Boston Circulatory Arrest Study found that up to 65% of 139 patients treated for D-transposition of the great arteries received remedial academic or behavioral services[5]. In our cohort, more than 7% of the total CHD cohort required special education or academic support services as compared to 0% of the controls. Although this proportion is lower than the outcomes of previous studies, it is still a significant and clinically meaningful finding. Such school related problems at young age may result in persistent academic difficulties throughout adolescence that may affect future academic achievement, career options and give rise to poor socio-demographic outcome[21]. On the CBCL problem scales and *DSM-IV*-oriented scales, parental scores for patients differentiated from matched controls on various domains of the behavioral spectrum. Results suggest that problems are particularly situated in the internalizing domain with more withdrawn/depressed behavior, somatic complaints, socialization difficulties, and thought problems. In addition, on the DSM-derived problem scales, parents of CHD-patients indicated more affective problem behavior, anxiousness, and more symptoms that relate to post-traumatic stress disorder. Although these results point in the direction of internalizing behavior spectrum, patient's parents also reported significantly more aggressive behavior.

Contemporary research has identified internalizing problems to be particular prevalent among populations with chronic illness[22], including those treated for CHD[4, 7]. This tendency to direct negative emotions inward can make it difficult to cope with unknown and stressful situations. Social withdrawal, anxiety, somatic complaints, and depressive symptoms characterize the behavioral profile of children treated for various forms of CHD[4, 7]. Poor emotional regulation at preschool age in terms of negative and irritable emotional tone, poor adaptability, and irregular or unstable self-regulation is speculated to manifest itself at later age in more

widespread problems of self-regulation in complex CHD survivors[23], and thus might precede internalizing behavior problems during childhood.

Poor emotion regulation might stem from aberrant mother child attachment mechanisms[24]; in light of the diagnosis and treatment, some mothers may feel insecure and not fully competent to take up care for a child with a chronic disease. Mothers devote more time and effort in the upbringing of a sick child, balancing with the care of possible other children. Daily tasks (regular medical check-ups, physical limitations, antibiotics for dental treatments) might give rise to recollections of the anxiety they felt regarding child's life-threatening medical history and impede healthy attachment processes. The emotional connotation attached to the heart may further exacerbate the parent's psychosocial and emotional maladustment[25]. Anxious and avoidant attachment displayed by mothers of CHD children causes intergenerational transmission of emotional problems; the mother is less sensitive and responsive to the child's distress signals and contributes to emotional difficulties in the child[24, 26]. Since children's regulatory functions, including their stress-response systems is directly influenced through their relationships with their primary caregivers[27], this reduced emotional availability and high levels of stress within the household causes children to identify with their mothers' distress and develop a negative selfconcept[24].

Weaker emotional resilience might relate to impairments in social cognition that have been described in CHD populations. Calderon et al. reported that, although facial expression recognition is relatively preserved, children treated for D-transposition of the great arteries display difficulties in age-expected comprehension of complex affective mental state (understanding of desires, attributions about other's false belief with regard to real events-first order false belief-, and difference between outwardly shown and inner emotions)[28]. In addition, poor socialization could emerge as a consequence of motor problems in cohorts treated for CHD; physical restrictions or parental concerns may cause reduced participation in activities requiring significant physical effort, limit interaction with peers, and impair socialization skills[3]. Although the parents of our patient cohort regard their child as socially competent with sufficient activity participation (hobbies) and a certain number of friends, they also report socialization difficulties such as not feeling accepted by peers, being teased a lot, and the tendency to cling to adults or the preference for younger children instead of

peers. These problems might stem from past multiple hospitalizations (UVH patients) whereupon they are not able to fully participate in peer sports and other social events, hampering social interaction and peer acceptance.

Patients treated for CHD scored significantly higher for PTSD on parental CBCL-ratings. This scale is based on PTSD symptomatology of the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV)[29] and incorporates a developmental perspective that states that a posttraumatic stress response in a paediatric population among other criteria includes re-experience (through play), avoidance (withdrawn behavior), and arousal (angry, irritable behavior). Paediatric hospitalization with intensified paediatric intensive care monitoring is a frightening experience for young children and may trigger anxiety, fear and other PTSD symptoms[30]. The scores of this scale might be inflated by other forms of anxious behavior or internalizing symptoms. A significant risk of PTSD after cardiac surgery in infancy or early childhood has been described before[31] and should be addressed by multidisciplinary teams supporting the developmental processes of children with CHD.

Although hospitalization or surgical management factors only marginally predict behavioral outcomes[12], there might be a genetic predisposition for neurobehavioral issues. In a prospective observational study, Gaynor et al. found that CHD populations that carry the APOE Є2 allele are at increased risk for displaying somatic complaints, pervasive developmental problems, internalizing behavior problems, and impaired social skills at the age of 4[9]. It is suggested that this type of genotype-environment interaction may be accountable for the interindividual variation in neurobehavioral outcomes following treatment for CHD[9].

Our results are clearly in line with previous studies identifying higher risk for psychosocial maladjustment in these clinical cohorts. These behavioral and emotional problems may aggravate throughout adulthood and result in psychopathological symptoms. Kovacs et al.[32] reported on the prevalence of depression and anxiety in adult patients treated for CHD. In a subset of 58 patients of the total cohort patients (n=280) evaluated at a mean age of 32 years, approximately 50% of the interviewed patients met diagnostic criteria for at least one lifetime mood or anxiety disorder, irrespective of cardiac defect complexity.

Rather than medical variables such as defect complexity or functional status, social adjustment and patient-perceived health status were predictive of depression or anxiety symptoms. This is a striking finding since lifetime prevalence of mood and anxiety disorders in a non-clinical population is estimated at 13-14% in Europe[33]. These alarming results suggest that the risk for psychopathology in this population is currently underestimated and undertreated. More attention should be directed towards psychosocial needs of this clinical cohort to promote a comprehensive understanding of possible genetic, medical, psychosocial and environmental predictors.

It might also be that parental responses were particularly tinged by own internal processes since paediatric cardiac surgery and hospitalization can be an important stressor for children but also for their parents. Studies have demonstrated higher stress levels in parents of children undergoing elective cardiac surgery, causing symptomatology adhering to Post-Traumatic Stress Disorder (PTSD)[34]. Several studies reported that parents of CHD patients, who experienced high levels of stress, noted more behavioral problems in their children[12, 35]. Parental stress in response to treatment for CHD is a non-negligible factor when considering behavioral issues in this clinical population. Surprisingly, we did not find major differences between patients who were treated for UVH or BiVH. One would expect that parents of patients requiring phased surgical palliation and multiple hospitalizations experience more stress and thus perceive their child as more vulnerable. On the other hand, these parents may be better informed and receive extra support from their social network or health practitioners to cope with this stressful situation.

Furthermore, upon initial diagnosis, followed by hospitalization and treatment, parents of patients perceive their child as more vulnerable[36] and adopt an overprotective, overindulgent alert attitude towards their children that may lead to difficulties with setting limits[37]. This strategy led by perceived vulnerability can in turn influence the parent-child relationship; disobedience, irritability and discipline problems may follow[38]. Later individualization processes may be affected and parents unintentionally influence autonomy and progression into independent adulthood in a negative manner. This overprotective nature of parenting, together with disease-related physical restrictions, school absences, and learning difficulties at a young age may facilitate social exclusion through promoting avoidance

behavior for potentially stressful activities. Such a chain of events may hinder socialization skills with peers, and potentially predispose them for social maladjustment and psychological distress. Today, such follow up and evaluation regarding parenting styles and emotional wellbeing in parents and CHD children is not standard practice, leaving these serious issues relatively unattended. This is especially lacking for those treated for a mild CHD condition, on the supposition that these children are functionally healthy and no adverse sequelae regarding neurocognitive and emotional development are expected.

In the follow-up Congenital Heart Disease Intervention Programme (CHIP)-School study, McCusker and colleagues studied the effects of parent- and family-based psychological therapies to promote social adjustment in children with CHD at school entry (aged 4-5 years)[39]. Results indicated therapy-related gains in maternal health and family functioning and children in the intervention group were reported as 'sick' less often and showed reduced school absence. Maternal mental health, worry, and child cognitive functioning were predictive for behavioral functioning almost a year later.

Taken together, these findings signal that it is clinically recommended and beneficial for both parent and child to address issues as parental stress, parent-child interactions and behavioral changes in the child during routine follow up, and particularly at key transition moments.

Such parental reports may be considered as a valid source of information regarding the child's overall cognitive functioning and psychosocial well-being, and may identify those patients at risk for developmental delays and refer them for broader neurodevelopmental testing and therapeutic services if indicated. In this way, we can be responsive to families' needs and organize our health system to coordinate the multifaceted treatment process consisting of extra tutoring classes, behavioral counseling, speech/language, occupational and physical therapies to optimize neurodevelopmental outcome and improve consistency in developmental follow-up across time. Guidelines on these specific issues have been provided by Marino et al.[40], suggesting that a partnership between parents, teachers and health care practitioners may be beneficial in recognition, risk stratification, and management of problems faced by these youngsters to maximize overall neurodevelopmental potential.

Study limitations

We reported on parental views on cognitive, emotional and behavioral functioning. Ideally, teacher reports would have been useful to complete and confirm the parental reports of their child's functioning at home and at school. Moreover, although instructions stated the questionnaire and the Child Behavior Checklist had to be completed by both parents, odds are very likely that in particular one parent filled out the questionnaires, giving a one-sided view of the child's emotional status and psychosocial functioning. The rather high rate of non-responders may have influenced our results through selection bias. Only parents of children who indeed noticed some problems in their child might have responded to our appeal to participate.

CONLCUSION

In conclusion, this study shows that in an era with advanced medical management of congenital heart disease, a proportion of patients may be at risk for persistent emotional and behavioral difficulties at school-age, hampering school competence, psychosocial well-being, and quality of life, and could suffer possible future psychopathology. Strengths of the study include a large sample size, a broad spectrum of various CHD diagnoses and treatments and an age- and gender matched control group with equivalent socio-economic background. Parental and teacher reports regarding school functioning are indispensable to gain better insight in psychosocial development and self-image in these youngsters. Unravelling factors in family dynamics, parenting and psychosocial development that contribute to these phenomena should be addressed by future research. Regular assessment, including parental psychological distress, family functioning, and careful review of depression or anxiety symptoms in the child during follow up evaluation seems advisable and may work advantageous to identify children at higher risk for psychiatric comorbidity when progressing into adulthood.

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CHAPTER 8

GENERAL DISCUSSION

GENERAL REMARKS

More than 60 years ago, less than 20% of children diagnosed with CHD reached adulthood[1], whereas nowadays up to 90% of these patients are surviving due to contemporary life saving management of the affliction[1, 2]. Along with advances in medical and surgical strategies in the detection and management of CHD, considered accountable for this growing number of survivors, came a growing concern for long-term academic and psychosocial challenges[3]. The major aim of this doctoral project was to explore the contributions of patient-specific and hospital-related factors on the neuropsychological and psychosocial profile of patients treated for mild or complex CHD. In addition, we wanted to evaluate and update the neuropsychological profile of mild and complex CHD since surgical and perioperative management have been refined over the last decades.

NEURODEVELOPMENTAL OUTCOMES & BEHAVIOR IN CHILDREN TREATED FOR CONGENITAL HEART DISEASE

Neurobehavioral functioning in children with a corrected septal heart defect

Many studies have focused on the long-term neurobehavioral profile of children with complex forms of CHD. The long-term development of children diagnosed with and treated for mild forms of CHD has been overlooked in contemporary literature. This left the question if these children are cognitively and behaviorally affected by the congenital cardiac anomaly and its treatment.

This was the rationale to perform extra analysis on an existing dataset exploring the neurocognitive profile of children treated for mild CHD.

In **chapter 3**, a patient subgroup was selected from a larger database of patients with varieties of congenital heart diseases treated between 1995 and 1999, investigated as a whole in a previous study[4]. More specifically, we evaluated neuropsychological outcomes and behavioral functioning of 15 school-aged (~8 years) acyanotic CHD patients, ASD-II and VSD respectively. Outcomes were compared to matched controls. In this patient group, we identified average intellectual scores, in accordance with previously published studies on preserved intellect in acyanotic CHD[5, 6].

The neuropsychological profile, as assessed by the NePsy, was mainly characterized by lower scores in visual attention, receptive language and fine motor skills compared to matched controls. These findings corroborate with the few studies on neurocognitive development in children with acyanotic CHD displaying inattention and impulsive task behavior[6, 7]. Oxygen-sensitive brain regions, particularly the frontal area, may be adversely affected by the cumulative effect of altered oxygen delivery after birth, extending until surgical repair[8] and/or through surgical management techniques such as CPB or DHCA[7].

This cohort scored also significantly lower in the language domain, in both productive and receptive language skills. These patients obtained lower scores in phonemic awareness (auditory phonological perception and analysis), which underlies efficient reading and spelling abilities[9]. They also displayed poor receptive language abilities, indicating poor processing and executing of verbal instructions.

These findings are in line with previous research where up to 25% of a CHD cohort treated for mild CHD did not reach normal expressive speech performance[10].

The clinical cohort performed worse than controls on tasks measuring fine motor skills, in particular with imitating bilateral static hand- and finger positions. Underlying inefficient visuospatial analysis, motor programming, and kinesthetic feedback from gestural positions may serve as an explanation of these results[11]. These findings support the vast majority of literature that gross and fine motor functioning is affected in CHD cohorts[3, 12-14]. Recent literature found that patients treated for simple or complex CHD need more time to start and execute their movement, such motor slowness at school-age[15] may result in poorer alignment and spacing in handwriting[16]. Presumably, altered or delayed brain development is suggested to account for this recurrent finding of suboptimal motor skills. Preoperative motor abnormalities are common[17], indicating compromised integrity of the central nervous system before entering the operating room. Links between motor functions and neurological structures have been identified. Atypical cortical folding of the left hemisphere central sulcus is associated to movement[18] and reduced total brain volume, including deviant white matter development, is suggested to be accountable for deficient motor functioning[18]. These structures may be particularly vulnerable for the additional effects of surgical management techniques, e.g. hypothermic circulatory arrest[19] or ECC duration[20]. Memory functions and visuospatial skills were not significantly different from controls.

Regarding psychosocial and behavioral functioning, evaluated by the CBCL (4-18 years), parental reports indicated problematic behavior in terms of withdrawn behavior, thought problems, social problems and attention difficulties. Although not statistically significant, up to ~47% of the parents of CHD children signaled school problems, 20% of the cohort repeated a grade and 20% required extra school services (special education or therapy).

These findings were rather unexpected since acyanotic CHD's are considered relatively mild, straightforward and easy to treat without additional late morbidity. From these findings it is clear that school functioning remains an area of concern in children treated for CHD. Assessments of cognitive and behavioral functioning in acyanotic patient cohorts is rather scarce, and contemporary research mainly focused on the neurobehavioral outcomes of children treated for cyanotic CHD. The

results in this study suggest that follow-up is warranted in this clinical population with seemingly normal outcome.

Neurodevelopmental outcome after surgery for acyanotic congenital heart disease

The results of the aforementioned exploratory study were a draft for more profound interest in long-term outcomes in acyanotic CHD cohorts. **Chapter 4** describes the neurodevelopmental outcome in a cohort of acyanotic ASD-II and VSD patients operated in a recent surgical era (1999-2010). The clinical population consisted of 18 ASD-II surgery patients and 28 VSD surgery patients. We compared the intellectual, neuropsychological and behavioral development of ASD-II patients to a group with VSD, 2-12 years postoperatively, and to performance of healthy matched controls. In addition, we collected hospitalization data, suggested by contemporary literature to be related to long-term outcome.

Regarding the *intellectual profile*, we identified a 15-point deficit in total estimated IQ scores in ASD-II patients when compared to matched controls. The *neuropsychological profile* of this cohort was mainly characterized by difficulties in inhibiting a former learned response, lower performance on expressive and receptive language tasks, subtle deficiencies in fine motor skills, lower scores in social cognition and visuospatial information processing. Parents of these patients reported more school problems than did parents of healthy controls.

Comparing outcomes of VSD patients with matched controls revealed similar average intelligence scores (no statistical significant difference), but a disadvantage for patients in neuropsychological domains of attention and visuospatial information processing. Simons et al.[21] reported that domains that mainly tap into visual cognitive processes were affected in a clinical cohort of VSD patients. Poor performance on visuospatial processing tasks have been found in the Boston cohort at a mean age of 8 years and is suggested to be caused by visual-perceptual deficits, a marker for poor mathematical skills[22]. Corroborating with the aforementioned study, von Rhein and colleagues demonstrated that deficient visual-spatial information processing persists at age ~14 and is not related to CHD diagnosis or surgical variables and reflects visuo-perceptual rather than motor control deficits[23]. These visual spatial tasks comprise broader higher cognitive functions, such as planning and organizational skills and suggest that children treated for CHD suffer a broad spectrum of subtle functional and interrelated deficits.

In our study sample, no differences were found on CBCL parental reports on *psychosocial and behavioral functioning* in both patient groups.

When attempting to identify associations with medical parameters, age at intervention and weight at intervention seemed to explain some of the variability in scores in both patient groups. As traditional associations between cognitive functioning and medical factors, such as ECC duration, cross clamp time, metabolic acidosis (pH<7.15), and duration of postoperative intubation[24] were not found, and SES was significantly associated with outcome scores, it becomes increasingly evident that socio-economic factors and parenting style contribute for a large part to long-term cognitive development[8, 25]. These findings contribute to our belief that even in 'mild' CHD, subtle neurocognitive deficiencies exist, irrespective of the treatment protocol.

Neurodevelopment and behavior after transcatheter versus surgical closure of secundum type ASD

In **chapter 5,** we studied the independent effects of treatment in a homogenous cohort of children diagnosed with ASD-II. The clinical cohort existed of 18 children treated surgically for ASD-II, and 30 treated via transcatheter-guided defect closure. In this manner, we could sort out the effect of CPB on patients' long term intellectual, neuropsychological and behavioral development.

Compared with the healthy matched controls, the total group of patients treated for ASD-II had a *neuropsychological profile* characterized by lower scores in attention and executive functioning, language, working memory, motor skills, social cognition and visuospatial information processing. Only subtle differences, mainly in visuospatial skills, were found between the surgical repair and transcatheter repair patients. Socioeconomic status, longer hospital stay, and larger defect size were significantly associated with adverse neurocognitive outcome scores. Parents of ASD-II patients reported more thought problems, post-traumatic stress problems, and lower school performance compared with parents of healthy peers when evaluating *psychosocial and behavioral functioning*. Again, we could not discern particular significant differences between patient groups. These results corroborate previous literature that children diagnosed with ASD-II display suboptimal neurocognitive outcomes[6, 26], but are in contrast with other studies that did not find any significant problems after invasive treatment for acyanotic CHD[5, 27]. The relative small sample size may have reduced the chances of finding significant

patient group differences. From this study, we can conclude that cardiac surgery with its techniques as CPB in ASD-II patients is not solely responsible for later adverse cognitive and behavioral functioning. Other patient-specific variables, pre- or postoperative factors, seem to contribute in larger part for the variability in long-term neurobehavioral development.

Neurocognitive development and behavior in school-aged children after surgery for univentricular or biventricular congenital heart disease

Chapter 6 focuses on the school-aged outcomes of children treated for complex CHD, such as HLH and TA. A cohort of 17 UVH patients was assessed with an extensive cognitive battery, 6 to 12 years after their first surgical intervention. Results were compared between subgroups (UVH, BiVH and a healthy control group). Associations between cognitive outcome, medical and socio-demographic factors were explored.

Mean intelligence and neuropsychological scores were found within normal ranges for all diagnostic groups. The *neuropsychological profile* of UVH patients was characterized by lower scores in auditory sustained and alternating attention, fine motor skills, visuospatial information processing, and to a lesser extent, memory performance. Regarding *psychosocial and behavioral functioning*, parents of UVH patients reported significantly more externalizing behavior, overall behavioral problems, suggesting difficulty in behavior regulation. School problems were also identified in approximately 47% of the cohort. No significant differences emerged when comparing behavioral functioning between UVH and BiVH patients. Total cumulative lifetime ICU stay, mechanical ventilation, but also patient-specific factors as pregnancy duration, birth weight and SES contributed to the variability in outcome scores. Only few differences were found in the neuropsychological profile of UVH patients or BiVH patients. UVH patients tended to obtain lower scores in memorizing and recalling facial characteristics, but performed better on directionality tasks. Over the years, many studies consistently agreed that adverse neurodevelopment was unequivocally related to CHD severity, that complex hypoxic CHD led to lower outcomes[28-30] but more recent findings show that intellectual and neuropsychological functioning between cyanotic or acyanotic (univentricular or biventricular) CHD is quite comparable[4, 31, 32].

Longer mechanical ventilation and prolonged stay in the pediatric intensive care unit were associated with cognitive outcomes and may reflect an eventful

postoperative course, requiring intensified monitoring. These factors have been associated with poor developmental outcomes by other studies[33, 34].

Our results suggest that neurodevelopmental outcome in non-syndromic children with complex CHD treated with surgical palliation is less compromised than expected, but parents and teachers should be attentive for signals that indicate cognitive difficulties to provide correct referral. Shortcomings in attention, fine motor skills and visuospatial information processing seem to persist in the neuropsychological profile of school-aged patients treated for complex CHD.

Long-term behavioral and emotional outcomes in school-aged children following invasive treatment for congenital heart disease: a multicenter experience

In **chapter 7**, we described the parental view on emotional and behavioral functioning of our total CHD cohort. Parents completed questionnaires on cognitive, emotional, and behavioral functioning. Parents of 94 patients treated surgically or via catheter-guided repair indicated reduced school performance, more need for special education, repeating a school year more often, and were experiencing significant school problems as compared to 94 age-, gender-, and SES matched peers. A significant body of literature has described the prevalence for need for special education or therapeutic interventions in more than 50% of patients with varying CHD complexity[14, 32, 35, 36].

On the cognitive and emotional questionnaire, patients' parents also reported significantly more problems in attention, fine and gross motor skills, and anxiety. Higher problem scores were found for *psychosocial functioning* in patients on CBCL ratings; withdrawn/depressed behavior, somatic complaints, social problems, thought problems aggressive problems, affective problems, anxiety problems, post-traumatic stress symptoms, and further on the composite scales internalizing problem behavior and total problem behavior.

Social withdrawal, anxiety, somatic complaints, and depressive symptoms characterize the behavioral profile of children treated for various forms of CHD[17, 37] Poor emotional regulation at preschool-age in terms of negative and irritable emotional tone, poor adaptability, and irregular or unstable self-regulation is speculated to manifest itself at later age in more widespread problems of self-regulation in complex CHD survivors[38], and thus might precede internalizing behavior problems during childhood.

These results suggest that in an era with advanced medical management of CHD, some patients may be at risk for persistent psychosocial problems at school-age, hampering school competence, well-being, and could suffer possible future psychopathology. Parental and teacher reports regarding behavioral/emotional functioning are indispensable to gain better insight in psychosocial development and self-image in these youngsters.

Summary of neurodevelopmental, behavioral and emotional outcomes

We examined the neuropsychological, behavioral, and emotional profile of 94 children subjected to infant cardiac surgery for CHD, 6 to 12 years postoperatively by comparing outcomes to that of a healthy age-, gender-, and socio-economic status matched control group. Parents completed behavioral checklists (Achenbach Child Behavior Checklist for Children aged 6-18) and a questionnaire regarding cognitive and emotional functioning. Preoperative, operative and postoperative hospitalization variables were retrieved from medical files to explore associations with long-term neurodevelopment.

Our results confirm that survivors of cardiac surgery in infancy are more likely than the general population to display learning problems, language difficulties, inattention and reduced social skills in combination with requiring more remedial services such as special education as consequence of reported school problems. Moreover, compared to a healthy control group, CHD children are more likely to display problem behavior predominantly in the internalizing spectrum.

Fig. 1, Fig. 2, Fig. 3, and Fig. 4 give a general overview of the neurobehavioral patterns in our total study cohort (94 CHD patients / 94 controls).

***Fig**. 1*

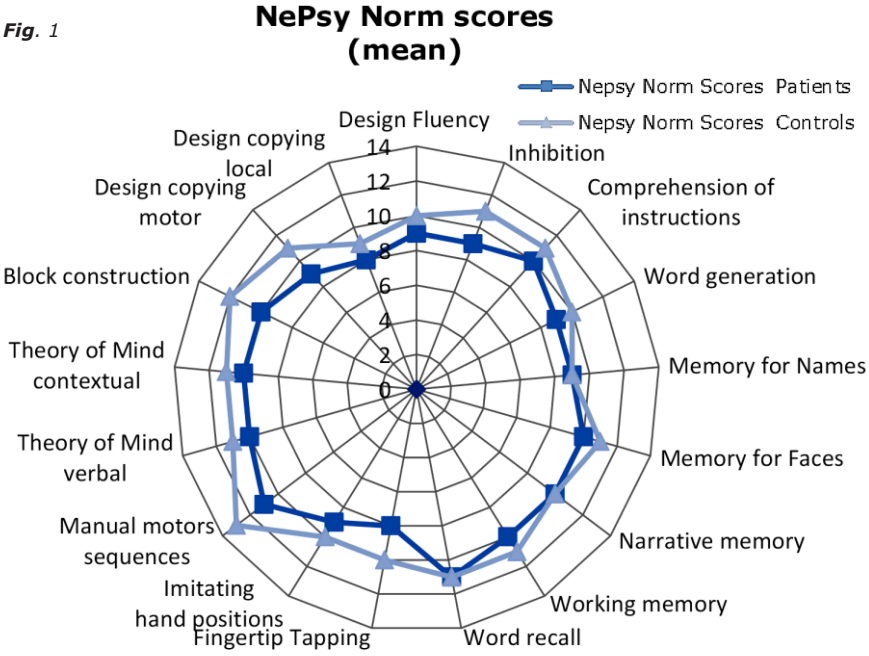
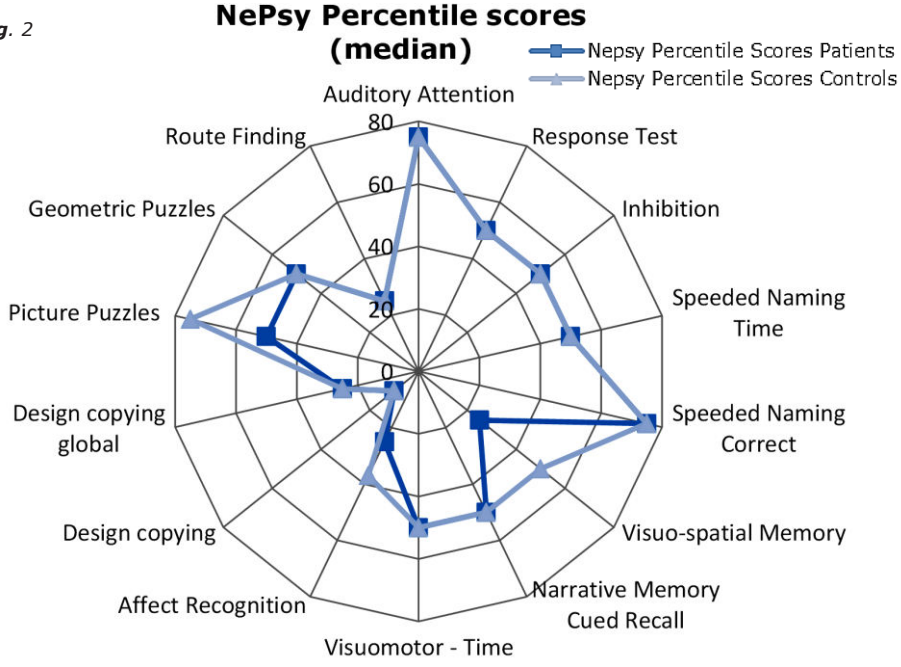
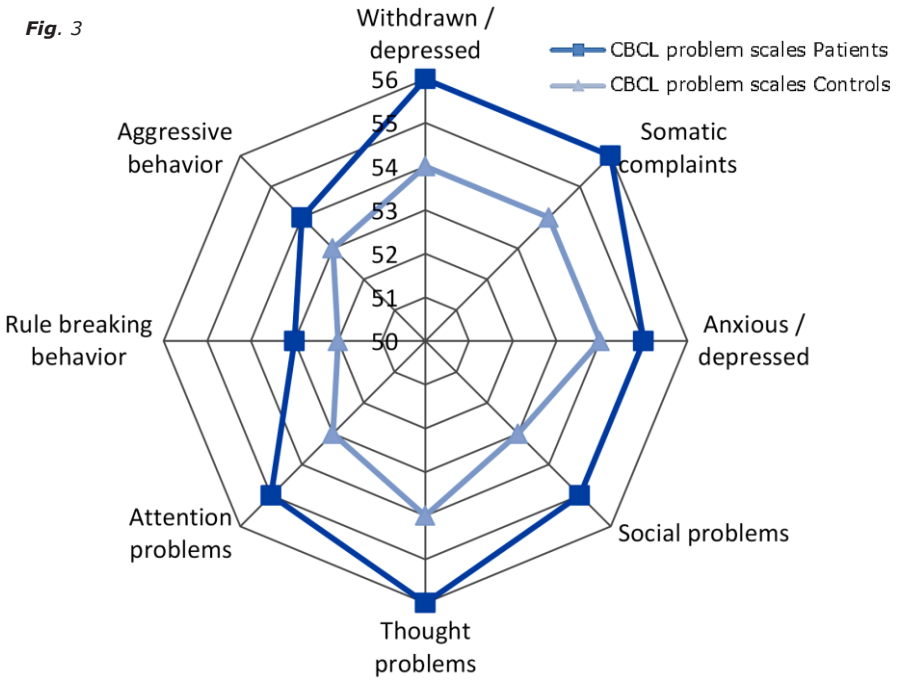


***Fig**. 2*



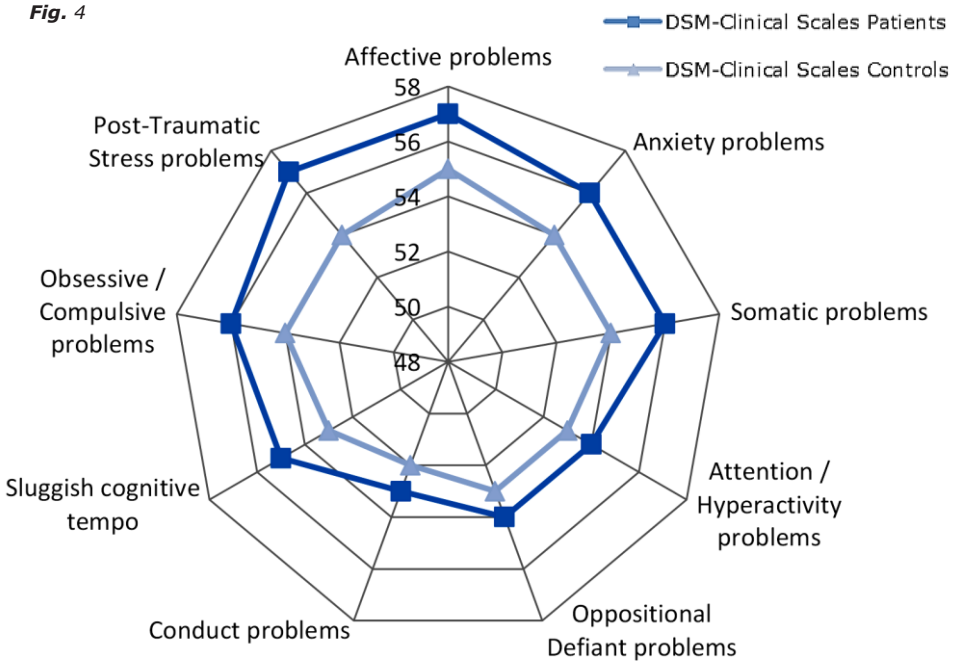
CBCL Problem Scales

***Fig.** 3*



CBCL DSM-Clinical Scales

***Fig.** 4*



**Note: Higher CBCL-scores reflect more problems as indicated by parents*

Our studies show that the neuropsychological profile of children with corrected septal defects (ASD-II or VSD) through surgical repair or catheter-based intervention is characterized by subtle problems in several domains. These patients scored lower on tasks of attention and inhibitory responses, expressive and receptive language, social cognition in terms of perspective taking, and performed especially worse on fine motor tasks and visuospatial information processing. Memory functions also appear involved, but to a lesser degree.

For patients subjected to phased palliation for univentricular physiology in infancy, the neuropsychological profile consisted of poor scores for attention, fine motor skills, visuospatial information processing, and to a lesser extent, for memory performance. The subtle neuropsychological deficits found in our patient cohort consist mostly of higher cognitive functions that are interrelated and depend on the integrative nature of subcomponents for adequate execution.

The parental reports on cognitive functioning in chapter 7 were accurately reflective of the objective neuropsychological performances throughout all studies regarding attention and executive functioning, memory and learning, and fine motor problems. Overall, these results are in line with findings from other (longitudinal) studies regarding the neuropsychological profile and the persisting nature of certain aspects, contributing to hampered educational attainment and other problems described in this patient cohort[6, 7, 10, 16, 17, 22, 24, 34, 39, 40].

The developmental signature of CHD does not only involve diffuse neuropsychological deficits, but also behavioral and emotional disturbances. Parents of CHD patients reported significantly more problems in predominantly internalizing, but also externalizing behavior. On a cognitive and emotional questionnaire, these parents also highlighted more problems concerning attention, fine and gross motor skills, as well as more anxiousness and health-related worrying in their child as compared to parents of healthy peers.

In response to the diagnosis, the invasiveness of CHD treatments, some parents may feel overwhelmed and insecure in the upbringing of a child with a chronic disease. After all, taking care of a sick child requires a significant devotion of time and effort, next to the care of other children, other household tasks, and work. These emotions of anxiousness and insecurities may give rise to inadequate parent-child bonding processes, such as anxious and avoidant attachment[41]. Decreased maternal warmth, emotional unavailability, insecurities, and worrying described in mothers of children with CHD may results in intergenerational

transmission of emotional disturbances within the child[41]. Although these mothers of children with CHD are not always capable of handling distress and anxious behavior of the child in a responsive and sensitive manner, they may perceive their child as particular vulnerable for developmental problems[42], leading to an overprotective parenting style[43]. These mechanisms of disturbed parent-child interactions may partly explain the current findings of increased internalizing and externalizing problem behavior throughout the individual studies.

Medical aspects related to the observed problems were defect size (for ASD-II patients), hospital and intensive care unit stay, duration of mechanical ventilation, birth weight and parental socio-economic status.

The complex interplay between genetics[44], aberrant neurological development resulting in delayed brain maturation[45, 46], together with possible clinically silent operative neurological events[47], hospitalization factors[34] and characteristics of family[33, 48] and parent-child mechanisms[41, 43] are suggested to be accountable for the diffuse nature of neurodevelopmental outcomes, behavioral and emotional disturbances seen in children treated for CHD.

These results in the mid-term outcome profile of children treated for CHD at school-age highlight the need for a multidisciplinary approach to follow up to aim awareness among primary caregivers, pediatricians and teachers that these children are at risk for developmental delay. This might lead to interventional programs with parental psychoeducational therapy and neurocognitive training attuned to the needs of the child and his/her family.

LIMITATIONS

Limitations of our multi-center cross-sectional study include possible selection bias and small sample sizes; probably parents of children who noticed some subtle problems in their child's cognitive or behavioral functioning, might have been more inclined to respond to our appeal. Refusal to participate could have underlying reasons of parents not wanting to confront the child with something that happened a long time ago when parents do not notice problems in cognitive or behavioral development. Our specific inclusion/exclusion criteria also might have prevented the most severely affected patients from participating, which may have led to an underestimation of developmental problems in patients with CHD. Larger sample size would have contributed to higher statistical power and enhanced extensive analyses. The retrospective character of this project might have prevented us for controlling for confounding factors that might have been present before the assessment and tinged current outcomes. Ideally, a longitudinal approach should be adopted to map temporal changes over time in cognitive development and assess the persisting nature of the described deficits. Brain imaging would have permitted us to determine if adverse neuropsychological functioning was associated with structural or functional brain injury in specific brain regions that are vulnerable for hypoxic-ischemic events (basal ganglia, frontal cortex, and hippocampus). In addition, the population-based Dutch norms for the NePsy-II-NL might be rather low for our cohort of Belgian children, overrating performance and possibly missing clinically meaningful observations. We did not control for parental overprotection, parenting style, or factors of parental distress, known to mediate neurodevelopmental, behavioral, and emotional outcomes, leaving us only speculating on the presence of such parental influences. Therefore, the combination of quantitative outcome measures together with a qualitative approach involving in-depth interviews with parents and/or teachers regarding the child's overall functioning at home, school, and in extracurricular activities would have allowed us to provide a more comprehensive evaluation of the child's psychosocial well-being and mental health and describe the whole system in which the afflicted child develops.

As stated before, obtaining a uniform perspective on neurobehavioral functioning in CHD patients has proven difficult. Numerous studies focus on multiple diagnoses and specific interventions in different surgical eras, study divergent age ranges, and use various screening instruments that may measure different aspects of neurocognitive domains. This limits the comparability and generalizability of

results and is the main factor in the conflicting findings obtained from this type of research. Nevertheless, extensive follow-up studies on neuropsychological and behavioral issues have conveyed consistent themes in the long term neurodevelopment of these children, validating the findings of this doctoral research project.

FUTURE DIRECTIONS

Ever since the first series of the Boston Circulatory Arrest Study considered surgical management factors to be accountable for adverse neurodevelopmental outcomes[49-51], over the last 2 decades numerous others followed to unravel the contributions of several intraoperative aspects with respect to cognitive and behavioral functioning in the early hope that modification in these factors would ultimately lead to improved mental and motor development. The majority of these studies however, have been disappointing because results were contrasting and unclear. Instead, in the last few years, it became increasingly evident that other factors outside the operating room contribute in a larger part to long term psychological development[25, 44, 52].

To improve developmental outcomes of this patient group, large multicenter prospective and longitudinal studies have to strive to reach consent in determinants for adverse neurodevelopmental consequences.

For instance the interplay with genetics should be assessed in a standardized manner to identify high-risk children. In this respect, the presence of the apolipoprotein E genotype has been associated with cognitive decline and behavioral problems after pediatric cardiac surgery[53, 54]. This might explain the interindividual neurodevelopmental outcomes and its association with proneness to impaired neuroresiliency. More studies should be conducted to confirm these hypotheses.

Delayed/altered brain maturation, has been found to equal that of premature newborns[46, 55], and is likely a direct consequence of the cardiac defect. In light of this, we can assume that preoperative altered structural brain development[18] and findings of perioperative brain injury[56-58] affect diverse brain regions and functions,

predisposing the young brain for injury susceptibility and may to lead long-term neuropsychological and behavioral problems.

The cause and location of brain regions that are particularly vulnerable for delayed/altered development should thus be further explored in relation to the neuropsychological profile. Magnetic resonance imaging and diffusion tensor imaging are prime research modalities to study such adverse neurologic development in CHD populations[59, 60].

Since age at surgery was found to be related to neurocognitive outcomes in our studies, we can assume that there are critical periods in brain development during cardiac repair or staged palliation. Determining developmental stages in which these children are particular prone for neurological injury would be helpful to minimize the impact of anesthesia and surgery. Consensus on timing of interventions for congenital heart disease should be considered not only in view of physiologic mechanisms[61, 62], but also in light of neurodevelopmental issues and ongoing brain development.

In addition, the knowledge of the neurotoxic nature of analgesic drugs and their influence on the young brain is accumulating[63] and associations with neurocognitive and functional outcomes are becoming more clear[64, 65]. Studies should address the exact contribution of and possibly determine a threshold for safe doses of analgesic drugs in children undergoing cardiac surgery to improve neurodevelopmental outcomes.

Since neurocognitive and behavioral development in children with CHD is not static, information on how these neurodevelopmental outcomes vary over time may be of great importance. Gaynor and colleagues[66] recently pooled published and unpublished data of 22 institutions to study temporal trends over a 14-year interval in 1770 children treated in infancy for complex CHD, assessed at preschool-age (mean ~14 months) with the Bayley Scales of Infant development, Second edition. They reported that both Psychomotor Developmental indexes and Mental Developmental indexes were lower in CHD patients compared to normative means and only changed moderately over time when adjusting for center, cardiac class and calendar year of birth. Predictor variables for lower scores over time include, lower birth weight, white race, presence of genetic or extra cardiac anomalies, lower maternal education, and male gender. They concluded that more high risk

patients are surviving nowadays and this growing population will require significant societal resources.

These findings imply that innate patient characteristics and possibly altered brain development due to the CHD and maturation outweigh the impact of modifiable hospitalization and treatment factors in assessing neurodevelopmental outcomes. Future studies should consider expanding these findings to neurodevelopmental variations over time in an older group, because early developmental testing has only limited predictive value for later functioning.

Educational and therapeutic interventions and psychosocial follow-up for parents when the child is diagnosed with CHD should be intensified. McCusker et al.[67] reported on a follow-up randomized controlled trial of psychosocial interventions to promote adjustment and family well-being in children with CHD and their families. Maternal mental health and family functioning improved significantly, and were predictive of the child's behavioral functioning almost a year later. These kinds of interventions are easily implemented in clinical paediatric cardiovascular programs and are useful to reduce stress, improve support, and promote family functioning.

Altogether, future research should try to resolve the identification of risk factors together with possible protective factors related to genetics, personality, parenting and environment in which these children thrive. Also, the later implications of these findings through adulthood in quality of life matters and possible career issues should be explored in the growing cohort of grown-ups with congenital heart disease (GUCH). For this reason, the healthcare system should see to it that facilities are being developed to provide multidisciplinary and specialized care for this increasing cohort as they grow older. In this way, a network of healthcare practitioners with expertise in congenital heart disease and all its features can establish a formal and cohesive congenital heart disease transition program[68]. Such integrative programs have already been implemented in cardiac centers in the United Kingdom[69].

Lastly, the integration of developmental psychologists in tertiary pediatric cardiac centers could prove beneficial to follow these children over time, make timely and proper referrals and provide psycho-education to parents to optimize adequate psychosocial functioning of the child and their environment[70]. Such

integrated care may alleviate the work load of pediatric cardiologists, since they only spend ample time with the patients during short follow-up visits and are not always able to address psychosocial concerns aside from the general medical check-up. Employing experts in psychosocial and neurodevelopmental sequelae commonly seen in these patients on site, in constant dialogue with the pediatric cardiologist, may help break down barriers and guide parents towards integrated psychosocial health care.

The questionnaire on cognitive and emotional functioning proved a useful instrument for parents to signal problem domains when these are surveyed in a semi-structural manner. The subjective ratings of deficits in cognition were reflective of the objective neuropsychological performances of the patient cohort throughout all studies. Moreover, we found satisfactory internal consistency of this questionnaire, which warrants further psychometric refinement to explore the usefulness of this instrument as a rapid evaluation of various domains of the cognitive, motor, and emotional developmental course of children afflicted with CHD during regular medical check-up.

The American Heart Association (AHA) and American Academy of Pediatrics (AAP) published the first comprehensive scientifically based statement for identification and risk stratification for children treated for CHD at risk for adverse neurodevelopment, taking protective factors, such as family and environment, into account[71]. Guidelines relating to medical and developmental surveillance, screening and periodic re-evaluation beyond infancy and early childhood are therefore clinically recommended and conformity should be strived for. The health care system should be reorganized in a way that children at risk and their families are supported by multidisciplinary teams consisting of the child's primary pediatrician, cardiologist, and developmental psychologist to coordinate the multifaceted treatment consisting of special education, behavioral counseling, speech/language, occupational, physical therapies and assessment of family functioning. Implementing these guidelines on the evaluation and management of neurodevelopmental outcomes in future research creates the opportunity to identify and treat children at risk and optimize full developmental potential.

CONCLUDING REMARKS

From this multicenter, multidisciplinary, and cross-sectional study we can conclude that, although intelligence is relatively preserved in CHD cohorts, the neuropsychological profile is mainly characterized by diffuse difficulties in attention, motor skills, and visuo-spatial processing which persist in school-age development. These problems impact school functioning and may put these children at risk for hampered educational attainment, future psychopathology, and career challenges. Literature across surgical eras and diagnoses have changed significantly; where the association between intraoperative techniques, and long-term cognitive and behavioral functioning was the focal point a few decades ago, variables more inherent to the patient, such as socio-economic status, intra-uterine brain development, and genotype seem to explain more of the variability in neurodevelopmental outcomes nowadays.

The chronicity of the condition of congenital heart disease should be acknowledged as surviving adults are increasingly outnumbering children with CHD, the persisting neurodevelopmental and behavioral problems will require significant societal resources in the near future.

In addition to a more thorough understanding of the neurobehavioral phenotype in these children, the results from this project advise multidisciplinary multimodal educational and therapeutic interventions to promote learning strategies to compensate for and remediate the reported difficulties. It is particular crucial to ensure that parents, teachers and health care practitioners are informed about medical treatment protocols, available psychological programs and advice, guidance to special educational needs as soon as concerns are raised regarding cognitive functioning or behavior. Disentangling the multifactorial nature of neurodevelopmental sequelae continues to be very challenging, but is also very promising by combining expertise from multidisciplinary fields in an effort to provide better health care and quality of life to those afflicted.

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SUMMARY

The worldwide birth prevalence of congenital heart disease (CHD) is estimated at 8-9 per 1000 births. Due to advanced medical care and therefore notable reduced postoperative mortality, focus of attention has shifted towards cognitive development, psychosocial well-being, and behavioral functioning of this patient group. Children with CHD have been found to cope with difficulties in areas of motor functions, perceptual organizational abilities, attention, information processing, memory, and poor language development. Furthermore, previous research showed a high incidence of behavioral problems and psychosocial maladjustment. Parents of patients rate their children as having more school problems, more social and attention difficulties, and more aggressive and impulsive behavior than children without CHD.

Initially, studies attributed neurodevelopmental sequelae in children with CHD to intraoperative support strategies such as cardiopulmonary bypass, pH management, and hemodynamics but it soon became clear that the etiology had to be multifactorial with preoperative, peri-operative and postoperative factors all contributing to outcome. Further, the integrity of the nervous system of these patients is questioned since brain imaging studies found alarming rates of preoperative and postoperative neurological damage in this cohort. These findings suggest a particular proneness for hypoxic/ischemic brain injury originating in utero and add to the culminating effects of adverse intraoperative or early postoperative events.

Children with corrected CHD are in need of specific attention since they obviously display neuropsychological difficulties that have long-term developmental repercussions. Up till now, the relation between these functional deficits and possible predictors is unknown and research results are inconsistent, so early identification of the children at risk for neuropsychological deficits remains a concern.

The purpose and goal of this doctoral dissertation was to provide a better insight in the prevalence and processes involved in the adverse neurodevelopment of children treated for CHD. We evaluated the neuropsychological profile, behavioral, and emotional functioning of 94 patients treated for univentricular or

biventricular CHD by comparing them to a healthy matched control group. We collected pre-, peri-, and postoperative hospitalization data to examine the selective and mediating influence of these factors on late developmental outcomes.

Compared with controls, the neuropsychological profile in patients treated for mild and complex CHD was characterized by subtle deficits in attention and executive functioning, language, working memory, motor functioning, social cognition, and visuospatial information processing. Parents of CHD patients described their children to be less competent in school, having worse school performances and having a higher incidence of repeating a school year. Problem behavior was common in the CHD cohort, with problems in both internalizing and externalizing behavior spectrum.

Concurring with these neuropsychological outcomes, parents of CHD patient reported significantly more problems in attention, problem solving, memory, fine and gross motor skills, and anxiety compared to parents of healthy controls. Medical aspects related to the observed problems were defect size, duration of hospital and intensive care unit stay, duration of mechanical ventilation, birth weight and parental socio-economic status.

These problems impact school functioning and may put these children at risk for hampered educational attainment, future psychopathology, and career challenges. These results in the mid-term outcome profile of children treated for CHD at school-age highlight the need for a multidisciplinary approach to follow up to aim awareness among primary caregivers, pediatricians and teachers that these children are at risk for developmental delay. Employing experts in neurodevelopmental processes in pediatric cardiac centers may provide a unique opportunity to assess developmental patterns over time, make timely and proper referrals, and provide psycho-education to parents to optimize psychosocial functioning of the child and their environment. As surviving adults are increasingly outnumbering children with CHD, persisting neurodevelopmental problems will require significant societal resources in the near future.

SAMENVATTING

Acht tot twaalf per duizend baby's worden gediagnosticeerd met een aangeboren hartafwijking (AHA), en vertegenwoordigen ongeveer 10% van alle aangeboren afwijkingen. Gezien de ernst van de medische toestand is een ingreep tijdens de eerste levensjaren vaak onvermijdelijk. De laatste 45 jaren is de pediatrische cardiologie en congenitale cardiochirurgie aanzienlijk geëvolueerd. Ondanks de toegenomen overlevingskansen beïnvloedt morbiditeit, voornamelijk in de vorm van neurologische abnormaliteiten en ontwikkelingsachterstand, het schools presteren en de levenskwaliteit van deze kinderen. Omdat de meeste kinderen de operatie(s) overleven, ontstaat steeds meer belangstelling voor de invloed van het hartprobleem en de operatie op de mentale ontwikkeling van het kind.

Uit voorgaand onderzoek blijkt dat kinderen met AHA een neuropsychologisch profiel vertonen dat voornamelijk milde motorische tekorten omvat alsook discrete taalproblemen. Aandacht -en executief functioneren, alsook het geheugen blijken betrokken te zijn. Bovendien geven de ouders aan dat hun kinderen minder schoolbekwaam zijn, minder goede schoolresultaten halen en het overdoen van een schooljaar komt significant meer voor in deze groep.

Het grote probleem is echter het tijdig identificeren van deze kinderen en daartoe dient de relatie tussen de gerapporteerde neuropsychologische tekorten en mogelijk geassocieerde medische factoren te worden bestudeerd.

De onderzoeksdoelen van dit doctoraatsproject bestonden erin na te gaan hoe het neuropsychologische en gedragsmatig profiel eruitziet bij kinderen met een 'milde' AHA. Het merendeel van voorgaande ontwikkelingsstudies richtte zich voornamelijk op resultaten van kinderen met een complexe AHA omwille van gebrekkige zuurstofvoorziening naar de hersenen door de aandoening in se en ingewikkelde chirurgie. In dit kader wilden we tevens nagaan of chirurgie met of zonder extracorporale circulatie andere effecten heeft op de neuropsychologische ontwikkeling dan interventionele technieken (katheterisatie) bij kinderen met een atriaal of ventrikel septum defect (ASD/VSD).

Een tweede onderzoeksluik bestond erin te evalueren hoe het neuropsychologische en gedragsmatig profiel van kinderen met een complexe AHA

zich aftekent. Meer specifiek wilden we nagaan of er een verschil is tussen de cognitieve ontwikkeling bij kinderen gediagnosticeerd met hypoplastisch linker harten en tricuspiedklep atresie na chirurgische correctie, mogelijk veroorzaakt door preoperatieve defecten in de cerebrale circulatie of door chirurgie aan de aortaboog.

Het derde luik betrof het verschil van de lange termijn resultaten in neuropsychologische ontwikkeling tussen eenvoudig biventriculair herstel (ASD/VSD) en univentriculaire palliatie.

Bij alle voorgenoemde onderzoeksdoelstellingen wilden we nagaan of pre-, per, of postoperatieve aspecten in de zorg en behandeling voor AHA een effect hebben op lange termijn neurocognitieve en gedragsmatige resultaten.

Via een cross-sectioneel en multicentrisch (UZ Gent & UZ Leuven) onderzoeksopzet bestudeerden we de neuropsychologische en gedragsmatige ontwikkeling van AHA kinderen. Een intelligentiemeting (WISC-III-NL) en een uitgebreide neuropsychologische screening (NePsy-II-NL) werden uitgevoerd op schoolgaande leeftijd (6-12jaar) bij 94 AHA patiënten. Resultaten werden vergeleken met een controlegroep (n=94), gematched op basis van geslacht, leeftijd en ouderlijke socio-economische status. Aan alle ouders werd gevraagd gedragsvragenlijsten in te vullen rond de frequentie van probleemgedrag, cognitieve moeilijkheden, motorische ontwikkeling en het emotioneel functioneren van hun kind.

Uit de resultaten blijken kinderen die chirurgie of katheterisatie ondergingen voor de correctie van een mild hartgebrek (ASD/VSD), een neuropsychologisch profiel te vertonen dat gekenmerkt wordt door een normaal intelligentieniveau, maar significante tekorten in verschillende neuropsychologische domeinen. Zo bleken deze kinderen significant lager te scoren op taken van aandacht, expressief en receptief taalgebruik (spreken en begrijpen) en sociale cognitie in termen van perspectief nemen en begrijpen van context, belangrijk voor sociale interactie met leeftijdsgenoten en algemeen psychosociaal welzijn. Deze kinderen scoorden opvallend lager op taken die fijn motorische vaardigheden meten en taken die visuo-ruimtelijk inzicht vereisen, belangrijk voor schrijven en reken-/plan-vaardigheden. Verschillen in uitkomsten bij patiënten die behandeld werden via chirurgie of paraplu-sluiting (katheter) voor een ASD werden slechts matig bevonden en geven dus geen uitsluitsel over techniek-voorkeur op basis van ontwikkelingsuitkomsten.

Na gefaseerde heelkunde voor een complexe aangeboren hartafwijking gedurende de eerste levensjaren (voor hypoplastisch linker hart of tricuspiedklep atresie), weerhouden we problemen binnen domeinen als aandacht, fijne motoriek en visuo-ruimtelijke informatieverwerking op schoolgaande leeftijd. Duidelijke verschillen tussen kinderen met een hypoplastisch linker hart en tricuspiedklep werden niet gevonden. Verschillen in uitkomsten tussen kinderen met een univentriculaire of biventriculaire AHA waren slechts matig.

Medische correlaten van deze ontwikkelingsuitkomsten omvatten de grootte van het defect (ASD-II patiënten), totale duur van hospitalisatie en verblijf op de dienst intensieve zorgen en de duur van postoperatieve mechanische ventilatie. Voornamelijk patiënt-specifieke karakteristieken zoals geboortegewicht en socio-economische status van de ouders lijken bij te dragen aan de interindividuele variabiliteit in ontwikkelingsuitkomsten bij kinderen met AHA.

In het algemeen rapporteerden ouders van AHA patiënten meer schoolproblemen en meer nood aan onderwijsondersteuning (bijlessen, logopedie, therapie). De ouders merkten eveneens problemen op in aandacht, motoriek en het emotioneel functioneren bij AHA patiënten.

Deze resultaten bevestigen dat patiënten die behandeld werden voor een aangeboren hartafwijking meer kans hebben dan de normale populatie op problemen die het schools functioneren en levenskwaliteit op een negatieve manier kunnen beïnvloeden.

Kinderen met een gecorrigeerde aangeboren hartafwijking verdienen dus de nodige aandacht aangezien zij objectiveerbare neuropsychologische tekorten vertonen die van invloed zijn op hun schools presteren. Met de inventarisatie van de cognitieve tekorten en een onderzoek naar de oorzakelijke medische factoren ervan beogen we een bewustmaking van deze problematiek en een mogelijke implicatie naar interventies toe om deze kinderen te ondersteunen in hun vroege ontwikkeling. Signalering tijdens de jaarlijkse medische controle, herkenning en erkenning van deze cognitieve, gedragsmatige en psychosociale problemen zijn belangrijke punten tijdens de langdurige nazorg bij deze patiënten.

Een multidisciplinaire aanpak voor deze patiëntengroep lijkt aangewezen gezien steeds meer patiënten de volwassen leeftijd bereiken door vooruitgang in de pediatrische cardiologie, echocardiografie en congenitale cardiochirurgie. Zij zullen

bijkomende maatschappelijke voorzieningen vereisen ter ondersteuning van hun ontwikkelingstraject en in hun latere schoolcarrière. Mogelijke tewerkstelling van experten in het ontwikkelingsverloop van deze patiënten in tertiaire pediatrische hartcentra, zou toelaten vroegdetectie van cognitieve en gedragsmatige problemen te bevorderen, risicofactoren te identificeren, alsook ondersteuning te bieden aan het kind en ouders (neuropsychologisch onderzoek, ouderlijke psycho-educatie en verwijzing). Op deze manier kan expertise opgebouwd worden in multidisciplinaire dialoog met alle zorgverleners en kunnen nieuwe interventies getoetst worden op effectiviteit om continue, duurzame en kwaliteitsvolle zorg te waarborgen.

APPENDIX

Klachtenlijst

In deze klachtenlijst worden u enkele vragen gesteld met betrekking tot de cognitieve en emotionele toestand van uw kind.
Lees aandachtig elke vraag en onderstreep of omcirkel het antwoord dat het best bij jullie kind past.

A. COGNITIEVE DIMENSIE

1 Volgehouden aandacht

1.1. Mijn kind heeft moeite om zijn/haar aandacht langdurig op iets (bv. studeren, spel, TV, ...) gevestigd te houden.

altijd / meestal / soms / nooit

1.2 Mijn kind heeft het moeilijk om een mentale inspanning (bv. studeren) langere tijd vol te houden.

altijd / meestal / soms / nooit

1.2.1 Mijn kind moet, vaker dan leeftijdsgenootjes, taken langzamer doen om ze goed te kunnen doen.

altijd / meestal / soms / nooit

2 Verdeelde aandacht

2.1 Mijn kind kan moeilijk twee dingen tegelijk doen.

altijd / meestal / soms / nooit

2.2 Mijn kind is snel afleidbaar

altijd / meestal / soms / nooit

2.3 Mijn kind reageert minder snel dan leeftijdsgenootjes op wat er rondom hem of haar gezegd of gedaan wordt.

altijd / meestal / soms / nooit

3 Geheugen

3.1 Mijn kind is vergeetachtig (bv. vergeet huiswerkopdrachten, turn/ zwemmateriaal)

altijd / meestal / soms / nooit

3.2 Mijn kind kan zich bepaalde dingen niet meer herinneren (bepaalde gebeurtenissen, gegeven opdrachten)

altijd / meestal / soms / nooit

3.3 Mijn kind kan moeilijk nieuwe informatie (bv. lesinhoud) aanleren en/of onthouden

altijd / meestal / soms / nooit

4 Probleemoplossend gedrag

4.1 Mijn kind kan moeilijk activiteiten plannen (geraakt snel in de knoei)

altijd / meestal / soms / nooit

4.2 Mijn kind kan moeilijk beslissingen nemen

altijd / meestal / soms / nooit

4.3 Bij een taak die bestaat uit meerdere stappen, heeft mijn kind moeite met de juiste volgorde

altijd / meestal / soms / nooit

5 Motoriek

5.1 Het geschrift van mijn kind is slordiger/ minder duidelijk dan dat van leeftijdsgenootjes

altijd / meestal / soms / nooit

5.2 Mijn kind heeft het moeilijk met fijn motorische taken (knippen, kralen rijgen, schrijven, inkleuren, enz.)

altijd / meestal / soms / nooit

5.3 Mijn kind heeft het motorisch moeilijker met lichamelijke activiteiten (zwemmen, lopen, turnen) dan leeftijdsgenootjes

altijd / meestal / soms / nooit

B. EMOTIONELE DIMENSIE

1. Emotionele stabiliteit

1.1 Mijn kind is prikkelbaar/opvliegend

altijd / meestal / soms / nooit

1.2 Mijn kind heeft last van stemmingswisselingen

altijd / meestal / soms / nooit

1.3 Mijn kind is neerslachtig, verdrietig

altijd / meestal / soms / nooit

2. Angst

2.1 Mijn kind is over het algemeen angstig (schrikachtig, op zijn/haar hoede)

altijd / meestal / soms / nooit

2.2 Mijn kind piekert/denkt veel na over zijn/haar gezondheid

altijd / meestal / soms / nooit

2.3 Mijn kind is rusteloos

altijd / meestal / soms / nooit

2.4 Mijn kind heeft last van slaapproblemen

altijd / meestal / soms / nooit

CURRICULUM VITAE

Personalia

Naam Iemke Sarrechia
Geboortedatum 17 april 1986
Geboorteplaats Sittard (NL)
Nationaliteit Belg
E-mail iemke.sarrechia@gmail.com
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Opleiding

2010-2014 **PhD candidate Life Sciences and Medicine**

Universiteit Gent - Universitair Ziekenhuis Gent
Dissertatie: Neurodevelopmental outcomes & behavior in children treated for congenital heart disease

2007-2009 **Master in de Psychologie** *(onderscheiding)*
Vrije Universiteit Brussel
Profiel/minor: klinische ontwikkelingspsychologie & biologische psychologie
Masterproef: Multipele spontane sociale inferenties: een onderzoek naar de neurologische correlaten van trekinferenties in interactie met doelinferenties.

2004-2007 **Bachelor in de Psychologie**

Vrije Universiteit Brussel
Profiel/minor: *Onderwijskunde & klinische psychologie: Cognitieve en Biologische psychologie*

1998-2004 **Latijn-Moderne Talen**

Koninklijk Atheneum Maaseik

Stage en Werkervaring

2015 Onderzoekscoördinator
Centre for Translational Psychological Research (TRACE)
In nauwe samenwerking met de faculteit Psychologie & Pedagogische wetenschappen KU Leuven en de dienst Psychologie Ziekenhuis Oost-Limburg (ZOL)

2010-2014 PhD candidate Life Sciences and Medicine

2009 Klinische Stage Centrum voor locomotorische en neurologische revalidatie (CLNR) UZ Gent

2008 Stage Laboratorium voor Neuropsychologie
Universiteit Gent

Algemene Competenties

Taal

	Nederlands	moedertaal
	Engels	zeer goede kennis
	Frans	basis
	Duits	basis

Informatica

Windows - Microsoft Office (Word, Excel, PowerPoint) – SPSS - Elektronisch Patiëntendossiers -Internet

Rijbewijs:

Type B

Academisch

A1

Sarrechia, I., Miatton, M., François, K., Gewillig, M., Meyns, B., Vingerhoets, G., & De Wolf, D. Neuropsychological outcome after surgery for acyanotic congenital heart disease. Research in Developmental Disabilities **2015**; 45, 58-68; doi:10.1016/j.ridd.2015.07.004

Sarrechia I, Miatton M, De Wolf D, François K, Gewillig, Meyns B, Vingerhoets G. Neurocognitive development and behaviour in school-aged children after surgery for univentricular or biventricular congenital heart disease. Eur J Cardiothorac Surg **2015**; doi:10.1093/ejcts/ezv029

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Vingerhoets, G., & Sarrechia, I. Individual differences in degree of handedness and somesthetic asymmetry predict individual differences in left-right confusion. Behavioral Brain Research **2009***; 204,* 212-216.

Sarrechia, I. Miatton, M., François, K., Gewillig, M., Meyns, B., Vingerhoets, G., & De Wolf, D. **2015.** Long-term behavioural and emotional outcomes in school-aged children following invasive treatment for congenital heart disease a multicenter experience *(Submitted)*

B1

Adolescents with congenital heart disease (Markus Schwerzmann, Corina Thomet, & Philip Moons)

Book Chapter: Neurological and psychosocial development in adolescence
Miatton, M. & Sarrechia, I. (2016)

Posters & Abstracts

Neuropsychological and behavioral functioning in children with a corrected septal heart defect. NVK Congress, 2010.

Lezingen

Neuropsychologisch en gedragsmatig functioneren bij kinderen met een gecorrigeerd septaal hartdefect. Nederlandse Vereniging voor Kindergeneeskunde, Veldhoven, 4 november 2010.

Onderwijsactiviteiten

Ontwikkelingspsychologie - 2de Bachelor logopedie/audiologie UGent
Cognitieve revalidatie en functionele plasticiteit - 1ste Master logopedie/audiologie UGent
Kinder-Neuropsychologische diagnostiek - 1ste Master experimentele psychologie UGent

LIST OF ABBREVIATIONS

AAP – American academy of pediatrics
aCHD – acyanotic congenital heart defect
AHA – American heart association
ApoE – apolipoprotein E
ASD(-II) – atrial septal defect (secundum type)
AVSD – atrioventricular septal defect
BiVH – biventricular heart defect
BSID – Bayley scales of infant development
CAVC – complete common atrioventricular canal defect
CBCL – the Achenbach child behavior checklist
CHD – congenital heart disease
CHIP – congenital heart disease intervention program
CICU – cardiac intensive care unit
CPB – cardiopulmonary bypass
Cr – creatinine
CRP – C-reactive protein
DAS – differential ability scales
DHCA – deep hypothermic circulatory arrest
DSM – diagnostic and statistical manual of mental disorders
d-TGA – dextro transpositions of the great arteries
DTI – diffusion tensor imaging
ECC – extracorporeal circulation
ECMO – extracorporeal membrane oxygenation
EEG – Electroencephalography
GUCH – grown-ups with congenital heart disease
Hb – hemoglobin
Hct – hematocrit
HLH – hypoplastic left heart
ICU – intensive care unit
IQ – intelligence quotient
IQR – interquartile range
LFCPB – low flow cardiopulmonary bypass
MDI – mental development index
MRI – magnetic resonance imaging
NePsy-II-NL – a developmental neuropsychological assessment, 2nd ed., Dutch version
PA – pulmonary atresia
pCO2 – carbon dioxide partial pressure
PDA – patent ductus arteriosus
PDI – psychomotor development index
pH – hydrogen-ion concentration (alkalinity)
PO2 – oxygen partial pressure
PTSD – post-traumatic stress disorder
PVL – periventricular leukomalacia
RCOF – Rey-Osterrieth complex figure
RCP – regional cerebral perfusion
SaO2 – oxygen saturation in arterial blood
SD – standard deviation
SES – socioeconomic status
SPSS – statistical package for social sciences
SvO2 – oxygen saturation in venous blood
TA – tricuspid atresia
TCPC – total cavopulmonary connection
TGA – transposition of the great arteries
TOF – tetralogy of Fallot
UVH – univentricular heart defect
VSD – ventricular septal defect
WISC-III-NL – Wechsler intelligence scale for children, 3rd ed., Dutch version

ISBN 978-9-4619733-4-4